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A TEXT-BOOK

OF

PATHOLOGY

BY

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Fourteenth Edition

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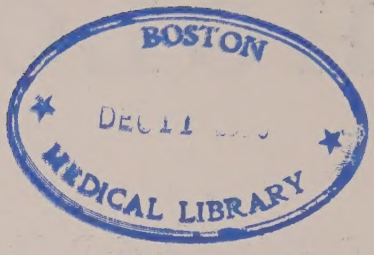
WITH TWENTY FULL-PAGE PLATES AND EIGHT HUNDRED AND THIRTY ILLUSTRATIONS IN THE TEXT IN BLACK AND COLORS

NEW YORK
WILLIAM WOOD AND COMPANY
MDCCCCXXVII



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Printed in the United States of America

THE MAPLE PRESS - YORK PA

PREFACE TO THE FOURTEENTH EDITION.

In the preparation of the manuscript for the Fourteenth Edition of Delafield and Prudden's Text-book of Pathology, I have endeavored to add to the text some of the more important developments in the subject of pathology which have appeared in the last few years. Aside from many detailed changes, especially new bibliographic references, the question of vitamins and hormones has been touched upon, changes have been made in the chapters on diseases of the thyroid, pancreas, lungs, and in that on the blood, while a consideration of some modifications in our conceptions of certain lesions of the liver and the gall-bladder have also been included. Additional matter has been inserted in the chapter on infectious diseases, in that dealing with the bones and joints, and that on the nervous system. A considerable number of illustrations have been added. The chapter on lesions following various types of poisoning has been eliminated from the text as these matters are covered much more fully and satisfactorily in the standard works on legal medicine than is possible in a text-book on pathology for students.

I had originally intended also to drop Part III concerning the method of making post-mortem examinations, but, yielding to the request of a number of teachers of pathology, have retained the first portion of this, omitting only that chapter on the preservation and staining of pathological tissues. This technic is given in detail in Mallory and Wright's "Pathological Technique," and Schmorl's "Untersuchungsmethoden," and as such technic is now rarely taught as an integral part of the general course in pathology, it seemed better to save space for other more important matters and refer those students who wish to fit themselves in this aspect of pathological practice to the larger and more comprehensive works.

I am glad to acknowledge my gratitude not only to my colleagues in pathology but to some of the anonymous reviewers for valuable suggestions in the revision of the text, and I wish to thank Dr. Robert T. Frank, Dr. Edward G. Cary and Dr. R. B. Cattell for aid in the preparation of certain portions of the revision, and especially Dr. Leila C. Knox for invaluable assistance in every phase of the work.

FRANCIS CARTER WOOD.

New York, *August* 1, 1927.

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PART I.

GENERAL PATHOLOGY.

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INTRODUCTION.

The successful pursuit of pathology—the science which treats of disease—depends largely upon the clearness and accuracy of the student's knowledge of the fundamentals of both gross and microscopic anatomy, of embryology, of biological chemistry, and of physiology. The possession of such knowledge by the reader is necessarily assumed in this epitomized presentation of a large and rapidly extending field of observation and research.

The Nature of the Living Body.—Leaving aside an accurate definition of life, as not indispensable, and at present not attainable, it is important constantly to realize that the normal living body is a complex and delicate mechanism incapable of creating new forces, but able, by means of its cellular and molecular organization, to accumulate or store energy derived from without, releasing this under fixed and definite conditions. This storing of energy is possible by means of the capacity of living body-cells to build up complex molecular combinations from simpler forms. The energy so stored in the cells may later be released by the fracturing of the complex molecules into forms of simpler type. Both the storing and the releasing of energy are largely bound up with the activities of the catalyzers or ferments present in the cell. This process it is which makes possible all expression of life.

The Chemistry of Life.—Some of the implications of this curious limitation of the composition of living matter are not without interest. Certainly it is worthy of speculation to consider why what is called "life" is a process taking place in a substance composed only of hydrogen, oxygen, nitrogen, and carbon, with traces of phosphorus and sulphur; that this living substance is even in the highest animals bathed with a fluid whose composition is suggestive of the ocean in which life must have originated. Without calcium and phosphorus locomotion in the air would be impossible. A trace of potassium in the red corpuscles seems to be fundamental. Sodium and chlorine contribute to the neutrality equilibrium of the blood and to the high acidity of the gastric juice. But more curious still in the elaborate animal forms is the vast importance to existence of minute quantities of other elements or substances. Three grams of iron permit the human being to breathe and live. One one-hundredth of this amount of iodine is necessary for continued existence. Fluorine, silicon, manganese, zinc, copper, arsenic, cobalt, aluminum, and even lead, are present in traces in the bodies of those living under modern conditions of civilization. As yet, however, the function of these last mentioned elements is undetermined.

There have also recently been discovered a group of five substances whose presence in the body in very minute quantities are necessary for

health and propagation of the species. They are assigned letters of the alphabet for as yet nothing is known of their chemical nature. The first to be discovered was the antiscorbutic vitamin C, the general qualities of which have been vaguely known for 200 years. This substance is present in fresh vegetables and milk. Germinating grains contain a considerable quantity. It is extremely fragile; boiling, or even pasteurization, of milk destroys it.

The second or water-soluble B was discovered by Hopkins.[1] It is the antineuritic substance which is present in abundance in yeast, fresh vegetables, the hulls of the cereals, grain, eggs and meat. The use of hulled rice or white flour as a diet may give rise to beriberi, a type of peripheral neuritis. This vitamin is soluble in water and withstands boiling.

The third in order of discovery is the fat soluble A. In 1913 McCollum and Davis found that by depriving animals of butter fat and fresh vegetables a condition known as xerophthalmia supervenes which is characterized by oedema of the eyelids, ulceration of the cornea, blindness, and ultimately death. The keratinization of glandular epithelium and it is claimed the production of cancer of the stomach in rats, has been noted when an animal is deprived of vitamin A.

Vitamin D is correlated with the development of rickets in children, hence has been termed the antirachitic vitamin. It is present in large amounts in cod liver oil. But rickets can be cured by exposure of the patient to sunlight or ultraviolet of a wave-length of about 3000 Å or shorter[2] which makes it difficult to account for rickets as an avitaminosis.

However it has been shown[3] that the ultraviolet irradiation of oils, in themselves not antirachitic, or of cholesterol, produced a substance identical with or metabolically equivalent to vitamin D. The isolation of this effective compound has recently been claimed.

But little is at present known of the fifth vitamin designated by the letter E. When animals are fed on a diet of casein, fat and starch to which has been added only salts and yeast they become sterile.[4]

Young, present in the uterus, atrophy and are absorbed. The testes of the males atrophy and spermatogenesis ceases. While small quantities of vitamin E are present in butter fat they are not sufficient to keep the animals fertile but if a small amount of wheat germ is added to the food or even if the oil which can be extracted from such germs is used sterility does not occur. This vitamin appears to be correlated with the proper assimilation of iron, the best form of which in such artificial diets is ferric citrate. It is suggested that the excellent results which have been obtained in the treatment of pernicious anemia with a diet rich in liver[5] may be due to the high content of this tissue of iron and of fat carrying vitamin E but this explanation is very questionable.

[1] *Hopkins*, Jour. of Physiol., 1912, xliv, 425.

[2] *Hess* and *Unger*, Jour. Amer. Med. Assn., 1922, lxxviii, 1596. *Hess*, *Pappenheimer* and *Weinstock*, Proc. Soc. Exp. Biol. & Med., 1922–1923, xx, 14.

[3] *Steenbock*, *Hart*, *Hoppert* and *Black*, Jour. Biol. Chem., 1925, lxvi, 441.

[4] *Evans* and *Bishop*, J. Metabolic Res., 1922, i, 319, 1923, iii, 233; also Jour. Am. Med. Assn., 1023, lxxxi, 889, *Simmonds*, *Becker* and *McCollum*, Jour. Am. Med. Assn., 1927, lxxxviii, 1048.

[5] *Minot* and *Murphy*, Treatment of Pernicious Anemia by a Special Diet, Jour. Am. Med. Assn., 1926, lxxxvii, 470.

The upset of the economy which occurs when the blood changes so slightly in its reaction that it cannot be detected by our familiar litmus paper may draw the line between life and death. A few milligrams of foreign protein injected under the skin of a person sensitized to that substance may cause death in a few minutes. The tortures of hay fever and certain types of asthma are produced by quantities of protein so minute as to be unweighable. If the pituitary gland, a mass not much larger than a pea, does not function properly, the individual may become a fat, impotent, useless creature, or a giant with malformed limbs and features. The absence of a small quantity of thyroid secretion makes a child an idiot. An excessive amount, probably of a perverted nature, may bring on a fatal thyrotoxicosis. A slight perversion of small areas of the pancreas makes the patient incapable of using glucose for the body's needs. These are a few examples only of the extraordinary delicacy but high efficiency of that mass of cells which we know as the human body. Health under these conditions seems more astonishing than disease and it is rather a matter to wonder that any individual survives to adult life, for in addition to all these substances which are required to keep the body in perfect condition, minute masses of protoplasm are continually invading the organism as a whole and either sensitizing it for fresh infections or setting up processes of the most far-reaching type. Only a few tubercle bacilli are necessary to change a healthy person into a chronic invalid, a few streptococci to irreparably ruin the kidney or cause death from scarlet fever.

The details of the chemistry of the life processes, so far as they are known, and their relationship to protein substances and protein metabolism in general, and to the highly specific enzymes, and a consideration of the successes, the hopes, and the dreams of the chemists within this borderland of living matter, belong in those studies in physiological and physical chemistry which naturally precede the consideration of the problems of pathology, and should be sought in special treatises.[1]

The Characters of Disease.—Many of the earlier views concerning life and death and health and disease, which have long since given way to more accurate conceptions, still hold a certain sway among the thoughtless, perpetuated by traditional forms of speech. One of these is that disease is an entity, something foreign to the body which may enter from without, and with which the body may struggle and fight, which it may conquer or to whose ravages it may succumb. It will be wise for the student constantly to remember that disease is not a thing, but a process. It is an abnormal activity of certain of the physiological functions of the body in response to an injury. This may or may not be associated with appreciable morphological alterations of the body structure. It is those

[1] See, for example, *Mathews, A. P.*, Physiological Chemistry, 2d edition, New York, 1917; *Hammarsten*, Lehrb. d. physiologischen Chemie, Wiesbaden, 1914; *Lusk, G.*, Science of Nutrition, Philadelphia, 1917; *Höber, R.*, Physikalische Chemie d. Zelle u. d. Gewebe, Leipzig, 1924; *Bayliss, W. M.*, Principles of General Physiology, London, 1924; *McClendon, J. F.*, Physical Chemistry of Vital Phenomena, Princeton, 1917; *Wells, H. G.*, Chemical Pathology, 5th edition, Philadelphia, 1925; *Robertson*, Physical Chemistry of the Proteids, 1918; *Bechhold, H.*, Die Kolloide in Biologie und Medizin, Dresden, 1912; *Abderhalden, E.*, Lehrbuch d. physiol. Chemie, 3d edition, Berlin, 1914, and Abwehrfermente, 4th edition, Berlin, 1914; *Sherman, H. C.*, Chemistry of Food and Nutrition, 3rd ed., New York, 1927.

agencies and conditions to which the body has not adapted itself, which, swaying its normal capacities now one way and now another, induce the functional aberrations and structural alterations by which disease is manifested.

It follows from this that the functional abnormalities and the structural alterations which make up the signs, symptoms, and lesions of disease involve the expression of no new functional capacities which the normal body does not possess. These may be diminished or exalted; they may be perverted or abolished; or the cells may now and then revert to forms and to phases of activity which the body has long since outgrown or largely suppressed in its slow adaptation to conditions of life which now constitute the normal. But the body in disease manifests no new functions, develops no new forms of energy, reveals no new capacities.

The Significance of Cells in Pathology.—If pathology is to be for the student or the practitioner anything but a mass of more or less useful facts he must learn to correlate its data with the facts and laws of normal morphology and normal physiology. While he should be conscious always, on the one hand, of the invisible molecular changes which underlie the manifestations of energy, and, on the other, will not ignore the details of gross morphology, his attention will be most constantly drawn to the cells as the life units upon which ultimately both the form and function of living things depend. He will realize that as the cells of the normal body are what they are in form and in function because of the conditions under which they have been slowly evolved, and are at the moment placed; so when the conditions change and become abnormal, it is to the cells that he must look for an understanding of the aberrations and disturbances by which we recognize disease.

In normal physiology attention is most keenly centered to-day upon the structure and performances of cells as the field richest in the promise of significant revelations. So, also, in pathology, by similar methods and with equal persistence, must the structure and performances of cells under abnormal conditions be studied if we are to hope with reason for a clearer comprehension of disease. This has long been recognized, and to the conception of the pathological processes as essentially cellular processes are due the great advances which this phase of biological science has made during the past few decades. But the newer knowledge of the cell, not as a membranous bag nor as a mere lump of protoplasm, but as a complex machine whose various structural features are of the utmost significance, has greatly widened the field of cellular pathology.

Nevertheless, the present swing of the pendulum is somewhat away from the hitherto dominant idea that the body is composed of a great mass of cells differing in function and, to a certain extent, independent of each other, and is turning more toward considering the cells as part of what might be termed a vast anatomical and physiological syncytium, each cell having its own physico-chemical activities, perhaps, but highly dependent upon its neighbors for existence and continued function. Tissue cultures, on the other hand, have shown that isolated cells, even

of the mammalia, can live in an artificial medium through a long period of time. This method, however, has not been hitherto as fruitful as was originally hoped, for the difficulties of growing continuously highly specialized adult tissues have been nearly insuperable. The methods of micro-dissection and micro-injection, while they have furnished material of immense interest to zoologists, have not yet yielded information of value to the experimental pathologist. As another example of the slowness of progress in these fields, we know but little more concerning the underlying conditions which cause a cell to divide than we did forty years ago, despite a host of explanations, mechanical, electrical and colloidal. So, too, despite an immense amount of study of the various elements of the cell, the nuclear structures, chondriosomes and other cytoplasmic segregations, we again have reached a point where progress seems difficult and the information accumulated to date almost infinitesimal in comparison with what we do not know of the functional activities of the cell. Nor have the most delicate procedures of biochemistry, such as the study of cell respiration and glycolysis, furnished complete insight into what lies behind this important energy-yielding process. The original assumption that these highly developed capacities were characteristic of neoplastic structures must be abandoned, for leukocytes and retinal cells possess the same capacity for anaerobic glycolysis as tumor cells.

Manifestations of heredity which are displayed in the body as a whole have long been known. To-day we may and must take account of the marks of heredity in individual cell life. Not a few of what we call the aberrances of cells in disease are but the expression of cell traits and capacities latent in the environment which has become the usual and therefore the normal, but finding expression as the sway of the body-organism is released under disturbances of its equilibrium. Thus cells thrown out of function may in a measure revert in character to types of a simpler structure, and cells long comparatively quiescent may, under varying stimuli, assume capacities and forms which they seemed to have outgrown.

Of course, in the pursuit of pathological morphology it is the dead body and dead tissues with which we are most often engaged. But these are of special interest only as they reveal structures or indicate processes which were maintained during life. So that he who can most closely correlate the knowledge of the living cells with his observations upon those which are dead will gain most from his morphological studies.

The Interrelationship of Cells and of Organs.—While the pathology of to-day is essentially a cellular pathology, while it is illuminating and convenient to consider the cells as physiological and structural units, maintaining a certain independence of existence and function, it is nevertheless true that beyond their mere juxtaposition in the body, beyond a close mutual dependence upon the common blood supply and nerve control, there is a subtle and as yet little understood transmission of physiological impulses from cell to cell. Whether this is often by protoplasmic continuity, by electrical or chemical[1] impulses carried by the nerves, or largely

[1] *Tashiro*, Am. Jour. Physiol., 1913, xxxii, 107.

by special agents or hormones present in the circulating fluids of the body, we do not know. But it should not be left out of the account in some of the more complex and subtle problems which, in health as in disease, the life of the cell and the life of the body present.

The interrelationship of organs, and the innervation and circulation which they share in common, have most important bearings upon both the morphology and physiology of disease. This relationship will be considered briefly in the later chapters of this book, but should receive especial attention in the study of clinical pathology.

The Excitants of Disease.—When we study the so-called *causes* of disease, we should remember always that, underlying the manifestations of disease, as well as sustaining the correlated processes which we name health, are the complex and ceaseless chemical transformations which in both health and disease alike supply the energy which sustains all expression of life. So that what we are wont to call the causes, whether external or internal, of disease are really not primary or efficient causes, but liberating impulses or excitants which sway and modify the orderly transformations of energy constituting health, with those manifestations of perturbed function or altered structure, or both, on which our conceptions of disease are framed.

Phases and Classifications of Pathology.—Pathology, then, deals with the disturbances of function and the alterations in structure in living beings, induced by unusual agencies and conditions. The functional disturbances thus induced are embraced as symptoms of disease in *physiological* or, far better, *functional pathology*, which so largely dominates the scientific activities of the physician and forms the basis for the practice of his art. The phenomena of pathological physiology are in no sense opposed to those of normal physiology, but are their inevitable correlatives when the living body is placed under sufficiently abnormal conditions. *Morphological pathology* is concerned with the structural alterations of the organism which may result from abnormal conditions. Morphological pathology deals with both the gross and the microscopic alterations of structure, and hence embraces both *pathological anatomy* and *pathological histology*.

But alterations in structure are so closely associated with disturbances in function, and both are so constantly dependent upon the inciting factors in disease, that an intelligent study of morphology necessitates a constant consideration of etiology and of certain phases of pathological physiology.

It is customary and convenient in the study of pathology to consider together the general or elementary abnormal processes and conditions and the etiological factors in disease without reference to their special manifestations in particular organs or parts of the body. This division of the subject is called *General Pathology*. *Special Pathology* deals with the forms and details of lesions in individual organs or parts of the body.

Correlated Sciences.—The human body is so complex in its organization that the student of pathology, like the student of normal morphology

and physiology, is under the constant necessity of seeking light through the study of simpler organisms. In our extremely differentiated and intimately coordinated cells, many features fundamentally simple are veiled or modified; so that we can understand them only when we interpret them in the light of less advanced forms. In other words, the results of this differentiation, by which we mean the formation and localization of many different kinds of substances out of the relatively simple structures of the primitive cell, are so complex that we must turn to simpler types with less highly organized structure and more constant environment than exist in the mammalia. For this reason many of the most important discoveries concerning fertilization have been made on the free-swimming sexual cells of the sea urchin and other similar marine forms.

Thus it is that in the lore of the zoologist and the botanist we may find the key to obscure and important manifestations of aberrant cell life. It is, in truth, through the pursuit of *comparative pathology* that some of our greatest advances in the conceptions of disease have been won, and in it lies much promise for the future. With the help of embryology, many obscure pathological conditions may be better understood. The highly developed technical methods of physiology and pharmacology, also, have been most valuable by placing in the hands of the experimental worker in pathology apparatus already perfected for purposes but slightly different from his own.

But it is to chemistry, both of the cell and of the organism, in health and in disease, that the scientific physician looks most eagerly for the solution of the manifold problems of medicine which each day become more numerous and urgent.

It is not, however, only the biological form of chemistry which holds out promises for the future; its youthful cousin, the physical, is daily extending its interest in many aspects of medicine. For we are realizing more clearly that in those complex and subtle processes which we are wont to call vital, such physical factors as molecular constitution, surface tension, conditions of dispersion, osmosis and diffusion, electrical equilibrium, elasticity, and pressure, are of the highest significance and in our studies cannot be wisely ignored.

It is well to remember, however, lest any undue optimism lead to the notion that but little remains to be done, that biological chemistry is not yet directly concerned with the composition and intracellular transformations of living cells, but only with their decomposition products and the exchanges which go on between the cell and its environment. It is still, therefore, engaged with the interpretation of living processes in the terms of dead protoplasm or its dead products. Life still, as ever, escapes analysis.[1]

[1] For a discussion of these and cognate problems as related to pathology, see *Marchand* and *Krehl*, Handbuch d. allg. Pathologie, Leipzig, 1912; and *Bouchard* and *Roger*, Pathologie générale, Paris, 1912.

For interesting studies on the general biological methods of attack, using the lower animals, see *Child, C. M.*, Individuality in Organisms, Chicago, 1915; and Senescence and Rejuvenation, Chicago, 1915.

CHAPTER I.

THE CONDITIONS OF DISEASE.

Adaptation in Health and Disease.—The human body, like other living organisms, has acquired its present form and its varied functions through gradual adaptation to its environment.

The maintenance of the normal life of the body involves a normal mechanism and impulse to start with, and a constant and successful adjustment to the conditions under which it is placed. While the continuance of the state which we call *health* depends upon the approximate maintenance of the external conditions to which the body has become adapted, it should be borne in mind that the adaptive capacity of the body is in many ways so effective that it can maintain its normal structure and functions in spite of unusual surroundings and adverse influences. Thus, for example, the body can adapt itself, within the limits of what we call health, to alterations, deficiencies, or excesses of nutrient material; to varying extremes of heat or cold, moisture or dryness; to electrical tension; to animal and vegetable parasites; and to various poisons, both those which come from without and those which result from faulty metabolism. Beyond certain rather ill-defined limits, however, the adaptive capacity cannot go, and disease results.

Disposition to Disease.—The adaptive capacity may vary greatly in different individuals, depending upon age, sex, race, etc., so that adverse conditions which one individual can sustain without marked functional disturbance or structural damage may induce in another more or less serious disease. There is thus *disposition* and *relative immunity* to disease. For example, children are in general much more disposed to certain diseases than are adults; and the negro is more prone to develop keloid tumors than is the white race. This disposition to disease is not, however, always fixed, but may give way to immunity under conditions which we shall study especially in the acute infections.

Disposition to disease may be inherited and find expression through obvious structural abnormalities or through subtle functional defects, difficult or impossible to define or detect.

Classes of Disease Conditions.—The harmful conditions to which the body may be subjected and which incite disease may be divided into two classes, *external* and *internal*. We may thus speak of external and internal conditions of disease.

It does not fall within the scope of this book to enter upon a discussion of the many and varied conditions under which disease occurs, nor to place in array the many and wearisome phases of classification which have been more or less imposing or useful in the earlier days of

pathology and medical practice. We shall consider here only some of the more general conditions of disease, referring for a study of the details of the specific excitants to later chapters.

External Conditions of Disease.

Disturbances of Nutrition.—The body may suffer through excessive or deficient nourishment. Too much food may in certain, though not in all, persons lead to an abnormal accumulation of fat. Too much food or unsuitable food may lead to disorders of the digestive apparatus or it may lead to the production within the body of metabolic substances which seriously damage important organs.[1] There is much reason for believing that through such faulty metabolism forms of autointoxication may arise which damage the parenchyma of the liver and kidney, for example, so that structural as well as functional disorders arise.

On the other hand, through insufficient nutriment the fat may disappear, the voluntary muscle substance diminish, and the blood deteriorate.[2] Inanition may, however, occur in persons whose food supply is both abundant and suitable; for example, in structural or functional disorders of the digestive organs, in the insane, etc. Nutrition may suffer also in the absence of a sufficient amount of water or of proteins or of inorganic salts in the food.[3]

Air Supply.—Through the function of respiration a supply of oxygen is furnished to the blood in the recesses of the lungs, and excretory products are carried off. The failure of this function may be due to a lack of air bearing the oxygen or to some interference with the respiratory channels or mechanism. The failure of oxygen to reach the lungs in proper condition and quantity is followed by forcible respiratory efforts which mark *dyspnea*. A fatal suppression of respiration by the exclusion of air is called *suffocation* or *strangulation*. *Asphyxia* is a condition in which respiration is suspended, but the heart continues to beat. This condition is of frequent occurrence in the new-born, and is associated with many forms of disease of the respiratory organs. (For a more detailed consideration of asphyxia, suffocation, and strangulation see page 503.)

Occupation.—Many diseases are closely dependent in origin upon unsanitary conditions associated with occupation. The dusty air prevalent in many stores, factories, theatres, court-rooms, prisons, schools, etc., may damage the lungs directly and render them more vulnerable in the presence of pathogenic microorganisms. The high temperature and foul air common in many places of work or assembly may be serious predisponents to disease. Finally, the abuse of alco-

[1] For interesting studies in the effect of deficient dietaries, see *Mendel, L. B.*, Jour. Am. Med. Assn., 1915, lxiv, 1539; and numerous papers by *Osborne* and *Mendel*, Jour. Biol. Chem., 1912, xii, 473; 1915, xx, 351; 1915, xxiii, 439; 1916, xxv, 1; 1916, xxvi, 1.

[2] *Benedict, F. G.*, The Influence of Inanition on Metabolism, Carnegie Inst., Washington, Bull. 77, 1907; *Meyers*, Jour. Med. Research, 1917, N. S. xxxi, 51.

[3] Consult for details, *Lusk*, Science of Nutrition, Philadelphia, 3d edition, 1917; and *Wells*, Chemical Pathology, 5th edition, Philadelphia, 1925.

holic drinks and tobacco may be cited among many common excesses as agencies through which the conditions of disease are fulfilled.

Damage from Excessive or Deficient Heat.—Through the heat-regulating mechanism of the body a remarkable adaptation to moderate elevations of temperature is possible.[1] But the maintenance of life is incompatible with very high temperatures.

Local exposure to both extreme heat and extreme cold induces necrosis and various phases of inflammation of the tissues.

Death may be caused by the inspiration of smoke and flame; by the drinking of hot fluids; by the direct contact of flame or hot substances with the external surface of the body. It may be due to the direct effect of the agents, to secondary affections of the viscera, or to the exhaustion produced by long-continued inflammation and suppuration. Sudden death may occur after extensive burnings of the skin.[2]

It is usual to divide burns into four degrees: 1, erythema of the skin; 2, formation of vesicles; 3, formation of an eschar; and 4, charring of the tissue. In the erythematous stage, the only lesions are a reddening of the skin due to the widening of the capillaries under the influence of the irritation, edema of the subcutaneous tissue, and, later, separation of the upper layer of the epidermis in the form of scales. The second degree burn, in which vesicles are formed, shows on examination only large or small collections of serum which lie in the upper layers of the skin and push up the epidermis. The basal layers of cells may remain attached to the corium in mild cases. If the fluid is drained off, repair takes place in a short time with covering of the granulation tissue of the corium by new epithelium, and a return to normal conditions if the burn has not been too deep; otherwise the hair, sweat, and sebaceous follicles may not regenerate and the epidermis may remain thin and smooth, without the rugæ which are usually present in the normal skin. The section of such a scar shows that the normal papillary downgrowth of the epithelium into the corium has not been regenerated, but that the layer of epidermis is very thin, smooth, and of even thickness. Extensive changes of this type are noted only after suppuration has occurred, and not when the serum is absorbed aseptically.

In a third degree burn, that in which an eschar is formed, the upper layers of the skin are actually destroyed by contact with the burning agent, whatever it may be. The microscopic examination of such skin shows on the surface a mass of dead tissue, either brownish or blackish, and thrombosed vessels, with great injection of those of the deeper tissues. A very considerable edema separates the connective-tissue fibers of the corium. The area about the eschar usually shows burns of the first and second degree. When the necrotic area separates from the healthy tissue, suppuration is likely to take place with local and general sepsis, and the final results may be a deep ulcer with erosion of the larger vessels, thrombosis, and a consequent embolus of the various organs, and, at a later stage, amyloid degeneration of the internal viscera through the suppuration. As soon as the eschar has separated, the wound granulates and forms a dense scar, which may or may not be covered up with epithelium. Whether this occurs or not depends upon the size of the burned area, for the ingrowing epithelium will extend just a certain distance. The scar tissue in the skin causes contractures of various types, even in superficial burns. In every deep burn there is always a tendency for the tissue to break down and form ulcers later, even after complete epidermization has taken place. Very rarely a squamous-cell epithelioma or a sarcoma may develop in the scar.

The lesions of burns of the fourth degree do not differ essentially from those of the third. The surface of the skin is deeply charred; the lesions extend into the corium or the subcutaneous fatty tissue; and in consequence, the ulceration and scarring, if

[1] *Lee, F. S.*, Am. Jour. Pub. Health, 1912, ii, 863 (bibl.); Jour. Am. Med. Assn., 1914, lxiii, 1625, (bibl.); Science, 1916, xliv, 183.

[2] For a study of sudden death following severe burns, consult *Silbermann*, Virchows Arch., 1890, cix, 488 (bibl.).

the subject survive the injury, is much more severe. Recovery depends very largely on the area of the skin involved; where more than half the body is burned, even to a very slight degree, death is almost certain to occur. It is not possible to produce the appearance of a burn by heat applied to the skin after death.

After death from severe burns there is apt to be congestion of the brain and the thoracic and abdominal viscera. The lymph-nodes and the lymphatic tissues throughout the body may be swollen and the seat of endothelial-cell proliferation and necrosis. There is usually albuminous degeneration of the liver and kidneys; the spleen is swollen, and the seat of focal necrosis. Focal necrosis in the bone-marrow has been noted. There may be capillary thromboses, interstitial hemorrhages in the kidney, hemoglobinuria, and leucocytosis. These lesions indicate the presence of toxic substances in the body fluids, and thus the general condition may be regarded as an instance of autointoxication.[1]

Secondary lesions are not infrequent after severe burns. There may be edema of the glottis, pseudomembranous inflammation of the larynx and trachea, pneumonia, ulceration of the duodenum,[2] and pyemia with infarctions in the lungs, liver, spleen, and kidneys, and lesions in the suprarenal capsules.

The action of cold on the body causes both general and local changes, which resemble to a certain extent those caused by heat, although the internal changes are much less extensive. Locally, three degrees of injury by cold may be described: 1, an erythema of the skin; 2, a vesicular stage; and 3, an actual necrosis due to frost. The skin and subcutaneous tissue will bear a considerable degree of freezing if thawing takes place promptly, as is known to all who have used cold as a local anesthetic; if, however, the freezing has lasted beyond a certain stage, the tissues, when they thaw out, show the first degree of frost-bite. The skin, after the reaction sets in, is very much reddened and swollen. Microscopically, the vessels are dilated, and the tissues are edematous. After a few days, repair usually takes place, but the tissues remain sensitive for a considerable period, and fresh freezing generally results in a more severe lesion. This condition is what is known clinically as chilblain. These are chronically inflamed, usually sharply localized, swellings of the skin, which are caused by paralysis of the vessels, serous exudation, and inflammatory hyperplasia of the skin and corium. They are most commonly seen on the hands and feet, especially on the extensor surface of the joint or outer part of the foot, less frequently on the face, and are usually due to repeated light chillings of the skin, especially in wet weather. They occur most often in young people, especially anemic and poorly nourished individuals. If they are improperly cared for, ulceration may occur, but if well treated they usually heal spontaneously. The chief reason for the interest which they excite is their extreme painfulness on pressure.

In the second degree of frost-bite, the skin is violet or deep red, and is covered with vesicles, and there is stasis in the smaller arteries, which leads to exudation of plasma, to edema, and to the formation of the vesicles. The contents of the vesicles are usually colored with blood, rarely purely serous. Such a lesion may heal without serious alteration of the tissue, but if infection takes place, it may dry up and form the so-called mummified slough, with, later, demarcation from the sound tissue. Such gangrene occurs even if the temperature to which the tissues are exposed is not below freezing. It is due, as stated, to circulatory disturbances. If the cold is much greater the gangrene is due to actual killing of the tissues by freezing.

While exposure of the entire body to cold may cause death there is nothing characteristic in the post-mortem findings. The symptoms as reported by arctic travellers point to a general reduction of the activity of the body functions and cerebral ischemia with slowed respiration, low blood pressure and pulse rate, great somnolence, and, ultimately, coma. Recovery has been observed after the body temperature had fallen as low as 24°C.

[1] For a study of the visceral changes following extensive burns, consult *Bardeen*, Jour. Exper. Med., 1897, ii, 501 (bibl.); *McCrae*, Trans. Assn. Am. Phys., 1901, xvi, 153; and *Locke*, Boston Med. and Surg. Jour., 1902, cxlvii, 480 (bibl.). For additional bibl. on the effects of heat and cold, see *Krehl* and *Marchand*, Handb. d. allg. Path., vol. i, Leipzig, 1908.

[2] This phenomenon is extremely rare and by many is considered to be merely an accidental concurrence of ulcers of the duodenum with death from burns. For report of an undoubted case and discussion, see *Busse*, *Otto*, Verhandl. d. deutsch path. Gesellsch., 1914, xvii, 290.

Electricity.—*Lightning.*—A large proportion of the persons who are struck by lightning die instantly; but those who survive the immediate effect may recover quickly without serious injury. The more seriously injured may continue comatose or delirious for several hours, and then either die or recover; or they may die after some time from the effects of the burns and injuries received.

The post-mortem appearances are very variable. Sometimes there are no marks of external violence or internal lesions. Sometimes the clothes are burnt and torn, while the skin beneath them is unchanged. Usually there are marks of contusion and laceration, or ecchymoses, or lacerated, punctured wounds, or fractures of the bones, or superficial or deep burns. The track of the electric current may sometimes be marked by dark red arborescent streaks on the skin. Fractures are rare.

The internal viscera may be lacerated and disorganized from lightning.

Artificial Electrical Currents.—In death from powerful artificial electrical currents, either by accident, as in linemen and others, or in electrical executions, there may be local burnings of varying degree where the wires or electrodes come in contact with the skin. The clothes may be pierced with holes at the point of exit of the current. Internally there appear to be no marked or characteristic lesions, either gross or microscopical, in this form of death. Observations have been made of the occasional, not constant, occurrence on the floor of the fourth ventricle of small hemorrhages, the significance of which is doubtful. Other petechial spots have been noted beneath the serous surfaces of the endocardium, pericardium, and pleura, and on the spleen.[1] Some days after injury from high voltage alternating currents, gangrene may occur in a limb through which the current has passed. The phenomenon is due to an extensive endarteritis involving the endothelium and subendothelial tissues of the large arteries and resulting in the formation of extensive thrombi. The localization of the changes points to the vessels as being the best conductors of the current, for the surrounding tissue is spared.

Roentgen Rays and Radium.[2]—Since it has been shown that Roentgen rays and the gamma rays of radium are light rays of very short wave lengths, the finer mechanism of their action has been much studied. Apparently such light rays have the capacity to break up the atom in their passage through it and to set free ionic particles with a considerable velocity.[3] It is these negatively charged particles, and not the rays themselves, which act upon the tissues and induce destructive processes. The effect is primarily upon the nucleus without immediate interference with the life of the cell. Threshhold exposures stimulate division of the nucleus; large ones slow such division; still larger exposures kill the

[1] *Cunningham*, New York Med. Jour., 1899, lxx, 581, 615; *Jelliffe*, Peterson and Haines, Textbook of Legal Medicine, Philadelphia, 1904, i, 245.

[2] For general information on *x*-rays and radium, see *Rutherford, E.*, Radioactive Substances and Their Radiations, Cambridge, 1913; *Kaye, G. W. C.*, *X*-rays, 2d edition, London, 1917; *Colwell, H. A.*, and *Russ, S.*, Radium, *X*-rays and the Living Cell, London, 1924; *Janeway, H. H.*, *Barringer, B. S.*, and *Failla, G.*, Radium Therapy in Cancer, New York, 1917.

[3] See, for methods of photographing these ions as they are given off, *Wilson, C. R. T.*, Proc. Roy. Soc., Ser. A, 1911, lxxxv, 285.

nucleus, but do not act lethally upon the cytoplasm.[1] In ascaris, the dividing cell is at least eight times as vulnerable to radiation as that in the resting phase, the increased vulnerability being most evident in the metaphase.[2] Thus, it has been shown that embryonic chicken heart muscle growing in vitro will continue to beat for days after the nucleus has been killed by exposure to a lethal dose of radium.[3] The same is true also of trypanosomes,[4] which retain their motility, but cannot divide. Hertwig,[5] in a series of experiments on frogs' ova, demonstrated that with radium it is possible so to damage the nucleus of the ovum or spermatozoon that it cannot functionate with the nucleus of an untreated cell of the other sex, although the sperm still possesses the power of initiating the maturation division of the ovum or, if untreated, to cause division of the radiated egg and supply a male nucleus. In such cases the larva which develops is either male or female, depending upon whether the nucleus of the ovum or of the spermatozoon has been killed.

In mammalian tissues the cells of the blood-forming and lymphoid apparatus are the most sensitive to radiation. Other tissues and organs show varying degrees of susceptibility; next to the spleen and bone-marrow, the gonads are most easily influenced; the thymus, also, is very sensitive. The muscles, connective tissues, cartilage, bone, salivary and thyroid glands, and especially the brain are quite insensitive to any but very extreme and repeated exposures. Touch corpuscles and other terminal apparatus of the nerves seem easily killed.

The milder lesions produced by radium or Roentgen rays are most easily studied in the skin. Moderate exposures produce, after about ten days, an erythema with dilatation of the vessels, perivascular collections of leucocytes, and swelling of the capillary endothelium. The Malpighian layer of the skin is edematous, the cell nuclei are pycnotic and stain poorly, and later the cells may fuse to form syncytial groups. The sweat glands and hair follicles are edematous and surrounded by leucocytic infiltration. Restoration to normal takes place rapidly. If the burn is more severe, thrombosis of the vessels may occur with areas of hemorrhage. The cellular changes are more extensive, with great edema of the connective tissue. After severe burns complete restitution may not take place, but the epidermis may remain thin, the corium dense, with few vessels, and the hair, sweat, and sebaceous glands atrophic. A network of dilated vessels may persist under the skin. These areas of altered skin are very sensitive to further radiation, and are very apt to break down and ulcerate without apparent cause.

After excessive exposures to Roentgen rays or radium, there is very little tendency to heal; even skin grafts do not take well on the devitalized surface, the reason being chiefly the condition of the blood-vessels. The surface of such a burn is covered with a layer of granulation tissue,

[1] *Packard, C.*, Jour. Exper. Zool., 1915, xix, 323; 1916, xxi, 199.
[2] *Mottram, J. C.*, Arch. Middlesex Hosp., 1913, xxx, 98.
[3] *Prime, F.*, Proc. New York Path. Soc., 1916, xvi, 56. See, also, *v. Wassermann*, Deutsch. med. Wchnschr., 1914, xl, 524.
[4] *Halberstaedter*, Berl. klin. Wchnschr., 1914, li, 252.
[5] *Hertwig, O.*, Handbuch d. Radium-Biologie und -Therapie (Lazarus), Wiesbaden, 1913, p. 163.

which may be fairly firm and usually is infiltrated with large numbers of plasma or lymphoid cells. In the connective tissue are often found large cells with irregular nuclei in fairly close connection with similar strands of cells which extend down from the epidermis and lead to the suspicion that these cells are epithelial in origin. In general, however, they lie close to the surface. Occasionally, below the ulcerated area the tissue loses its inflammatory infiltration, except for occasional collections of lymphocytes and plasma cells, and assumes a very firm consistence. Fat areas may remain of normal appearance; nerve trunks show atrophy of the nerve fibers with the production of a large amount of connective tissue in the bundles. There may be scattered areas of phagocyted blood pigment from old hemorrhages. The connective-tissue sclerosis may reach an extraordinary degree; areas may be found where only a half dozen nuclei are visible in the field of a low power lens. The nuclei are also abnormal, with a small amount of chromatin either distributed throughout the entire nucleus or gathered in pycnotic masses; the latter is observed especially if the burn has been recently treated with *x*-ray with the idea of stimulating it to heal. But it is in the blood-vessels that the most striking lesions occur. There is an extraordinary thickening of all the vessel coats, leading in some places to complete obliteration of the lumen, while in others a small space may still remain patent. The hypertrophy seems to be chiefly in the subendothelial layers, the circular bundles remaining fairly well defined. The endothelial lining usually persists. The elastic lamina does not show at all clearly in those vessels which have undergone extensive alterations, but is broken up into small particles. Not every vessel is affected and, as a rule, the veins are less damaged than the smaller arteries. The devitalization of the tissue is due, therefore, to the diminution in the blood supply. These tissues, when incised, bleed continuously, as the vessels have lost their contractility.[1] (Figs. 1 and 1*a*.)

If epidermization does occur, the skin is thin and very apt to break down at intervals, even years after the burning has occurred. Carcinoma or sarcoma may develop, but are much more apt to follow repeated, non-burning exposures over a long period. The skin under these circumstances loses its flexibility and becomes thickened, with the formation of keratotic areas. These may appear and undergo spontaneous healing, only to reappear again. Ultimately, when the victim has reached the cancer age, malignant changes may develop in these keratoses, which, even before they alter their character, very closely resemble epitheliomata. Fortunately, with increased knowledge of the dangers of *x*-rays and radium, greater care is taken to protect the workers and patients, and severe burns or chronic irritation of the skin or sterility due to gonad destruction is a thing of the past.[2] (Figs. 1*b* and 1*c*.)

The changes in the morphology of irradiated tumors are much the same as those described as occurring in the skin.

[1] For a study of chronic *x*-ray dermatitis, see *Wolbach, S. B.*, Jour. Med. Research, 1909, N. S. xvi, 415.

[2] *Hesse, O.*, Symptomatologie, Pathogenese u. Therapie d. Röntgenkarzinoms, Leipzig, 1911; *Pfahler, G. E.*, Jour. Am. Med. Assn., 1914 lxii, 189; *Ordway, T.*, ibid., 1916, lxvi, 1.

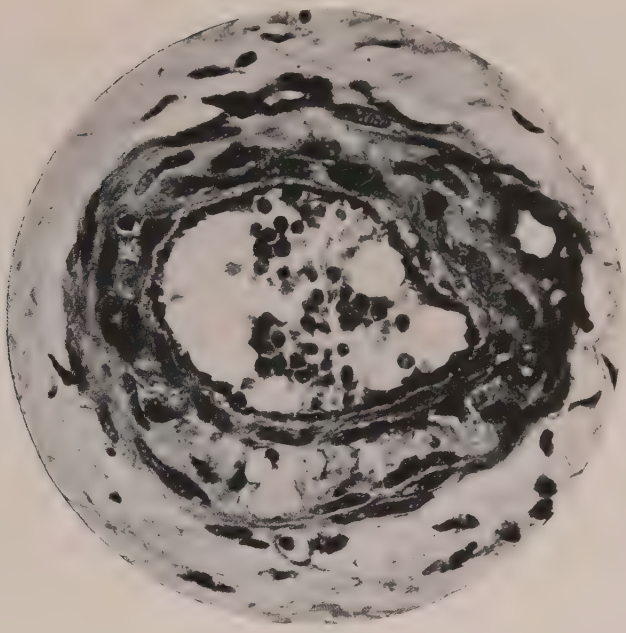

FIG. 1.—SWELLING AND EDEMA OF WALL OF ARTERIOLE 3 DAYS AFTER HEAVY X-RAY EXPOSURE OF THREE SKIN ERYTHEMAS. × 400.

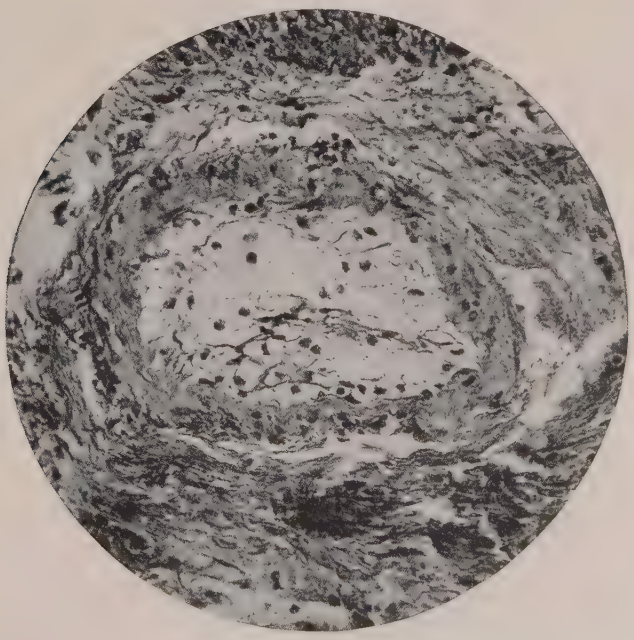

FIG. 1*a*.—COMPLETE OCCLUSION OF VESSEL FOLLOWING RADIUM TREATMENT OF A FIBRO-MYOMA UTERI. LATER STAGE OF FIG. 1. × 200.

Fig. 1*b*.—Epithelial Hyperplasia of the Skin of the Back of the Hand of an X-ray Operator. In This Stage the Growth is Not Yet Biologically Malignant and May Remain in This Condition for a Number of Years. A Certain Number of Such Precancerous Hyperplasias Ultimately Become Epithelioma. × 80.

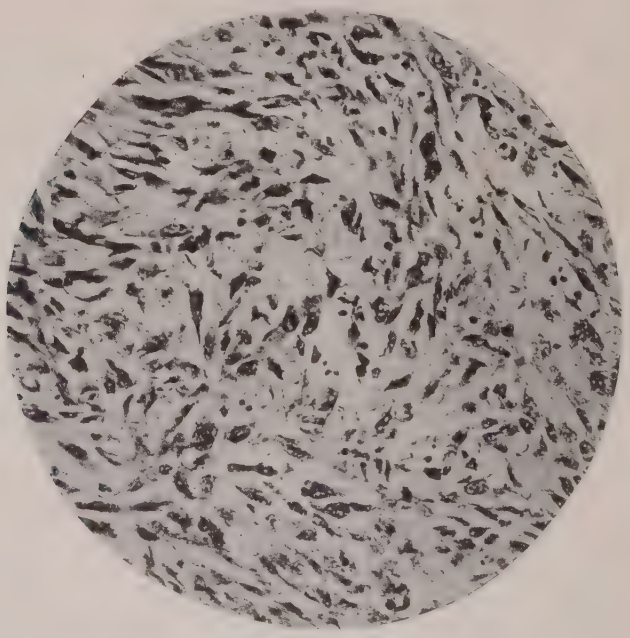

Fig. 1*c*.—Sarcoma of Lip Following X-Ray Treatment. × 200.

The mechanism seems to be threefold: 1, the direct lethal action of the rays on the tumor cells; 2, the obliterating effect on the capillaries producing ischemic necrosis of portions of the tumor; and 3, the blocking effect of the late connective-tissue sclerosis. Whether other factors enter it is premature to say. The production of an active immunity by stimulation of certain cells such as the lymphocytes, as claimed by Murphy,[1] is contrary to our experience in artificial immunity experimentally induced against the implantation of animal tumors, and seems not to be successful in the case of human neoplasms.

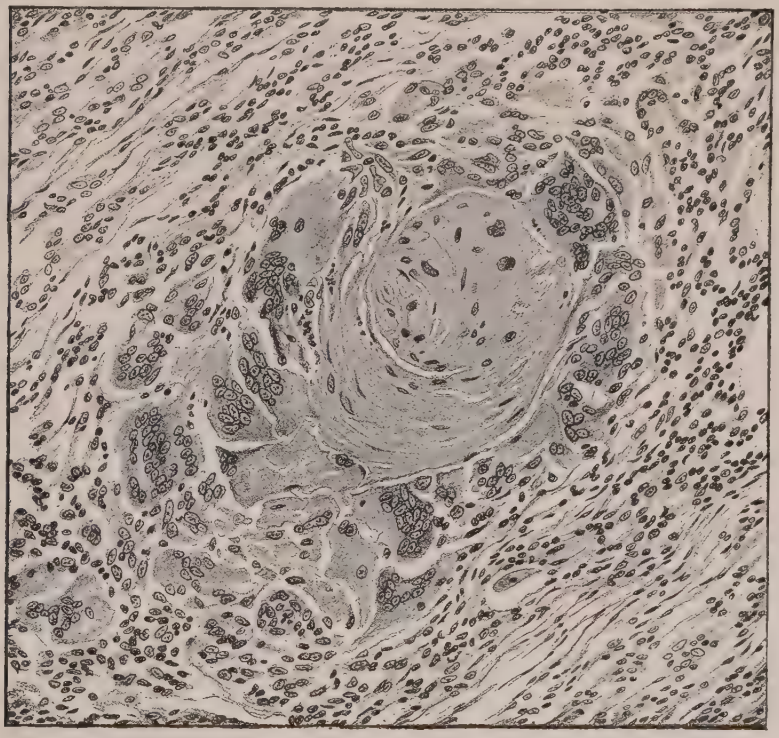

FIG. 1*d*.—PHAGOCYTOSIS OF SQUAMOUS EPITHELIUM IN CASE OF RADIATED EPITHELIOMA. Similar pictures may be seen in untreated tumors which are undergoing spontaneous regression.

The tumor cells show pycnosis and chromatolysis of the nuclei and tend to form syncytial aggregations. The latter are presumably due to paralysis of the mitotic apparatus with continued vegetative functioning of the cytoplasm. Occasionally, tumor cells can be seen undergoing phagocytosis (Fig. 1*d*) after their injury by radiation, but they are also unquestionably dissolved under the influence of the autolytic ferments and removed through the usual channels of the blood and lymph streams. Sudden shrinkage soon after treatment is often seen in very vascular

[1] *Murphy, J. B.*, and *Morton, J. J.*, Jour. Exper. Med., 1915, xxii, 204; *Loeb, L.*, Jour. Am. Med. Assn., 1915, lxiv, 726.

tumors and is due to thrombosis of the vessels with consequent necrosis of large areas of the tumor and absorption of the necrotic mass. At the periphery, where the tumor cells receive nutrition from the well-formed capillaries of the healthy connective tissue, survival of isolated areas of tumor is the rule, unless the exposure was sufficient to destroy the normal tissue also. As healthy granulation tissue is just as susceptible to the action of the rays as are growing cancer cells, there is probably no essential sensitiveness of the cancer cell over the multiplying normal cell of the same type. Practically the same degree of sensitiveness is observed in radiated tissue cultures of carcinoma, sarcoma, normal connective tissue, and epithelial cells. These facts point to the limitations of radiotherapy, for the successful destruction of a highly malignant neoplasm implies the serious damage of the surrounding normal tissues.[1] With

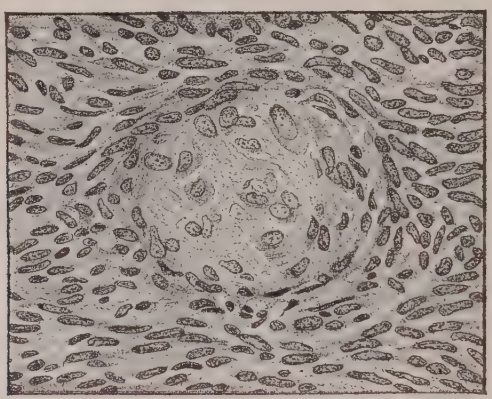

FIG. 2.—BASAL-CELL EPITHELIOMA OF THE NOSE SHOWING SMALL AREA OF SQUAMOUS CELLS.

The tumor was removed surgically after failure to cure with radium. The squamous cells resist the rays, while the basal cells do not—an evidence of difference in radiation sensitiveness even in tumor cells.

tumors of low virulence, such as the basal-cell epitheliomata of the face, the tumor cells may disappear before the healthy tissues are much damaged. The same is true of certain tumors, such as those of the uterus, where the remainder of the body is protected by the thick walls of the organ and large doses of radium can be given without excessive destruction of vital tissue. Similarly, the tumors composed of lymphoid cells (lymphosarcomata) are in some instances curable, as the lymphocyte is very much more sensitive to radiation than is the connective-tissue cell. A similar sensitiveness has enabled striking results to be obtained in the treatment of the chronic myelogenous type of leukemia, in which radiation of the spleen and bone-marrow may bring the circulating blood to normal and unquestionably greatly prolong the life of the patient. The lymphatic forms of leukemia and the acute types do not respond so well. After exposure of tumors or leukemic masses to radiation, the nitrogen,

[1] *Wood, F. C.*, Trans. Assn. Am. Phys., 1914, xxix, 430; *Wood, F. C.*, and *Prime, F.*, Ann. Surg., 1915, lxii, 751; *Prime, F.*, Proc. New York Path. Soc., 1916, xvi, 56; Jour. Cancer Research, 1917, ii, 107.

and uric and phosphoric acids of the urine are increased owing to the excretion of cell constituents.

Ultraviolet Light.—Light[1] of ordinary wave length has but little destructive effect on the skin or subcutaneous tissues, merely producing pigmentation, even though it is capable of passing through a considerable thickness of tissue, as is shown by the possibility of demonstrating the spectrum of sulphemoglobin through the palm of the hand when the latter is illuminated by sunlight. But if the tissues are sensitized by the injection of substances which very intensely absorb the rays of ordinary light, remarkable physiological effects may be produced. For example, if mice into which small quantities of hematoporphyrin have been injected are kept in a dark place, they remain in perfect health until the pigment is excreted in the urine; but if placed in the sunshine they die in convulsions in a few minutes.[2] Patients in whom a pathological amount of hematoporphyrin is formed have been noticed to suffer from skin lesions (*hydroa æstivale*) and even to show necrotic areas in the portion of the body exposed to light.[3]

These phenomena are based upon the well-known physical law that the chemical activity of the absorbed light is dependent upon the presence of absorption bands for a given wave length.[4] Thus, a photographic plate not ordinarily sensitive to green, becomes, when stained with erythrosine, a dye which has a strong absorption in the green portion of the spectrum, extremely sensitive to light of approximately the same region.[5]

As was first shown by Finsen,[6] ultraviolet light is very active in producing changes in the skin, though it penetrates only about 0.5 mm., but if the tissues are rendered bloodless by pressure, the same light penetrates nearly 5 mm. of skin, inducing inflammatory reactions at this depth. The protecting influence of the blood is due to its great absorptive power for ultraviolet light. The nature of the action on the tissue proteins is coagulative;[7] and the effect is not due to an alteration in the activity of the intracellular enzymes.[8] The susceptibility of the colorless cellular protoplasm or proteins in general to ultraviolet light seems to be conditioned upon the selective absorption of the rays by the aromatic amino acid radicals of the proteins. Such absorption bands were demonstrated forty years ago by Soret,[9] and recently Kober[10] has shown that tyrosin and phenylalanin have absorption bands in the ultraviolet;

[1] For a general review of the effect of light on the organism see *Jesionek, A.*, Lichtbiologie u. Lichtpathologie, Wiesbaden, 1912; *Bering, F.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1914, xvii[1], 790 (bibl.); *Clark, J. H.*, Physiological Reviews, 1922, ii, 277 (bibl.).

[2] *Hausmann, W.*, Über optische sensibilisatoren in Tier- u. Pflanzenreiche, Fortschr. d. Naturwissenschaft Forsch. (Abderhalden), 1912, vi, 243.

[3] *Ehrmann, S.*, Arch. f. Dermat. u. Syph., 1909, xcvii, 83; *Königstein, H.*, and *Hess, L.*, Dermat. Ztschr., 1910, xvii, 911; *Linser*, Arch. f. Dermat. u. Syph., 1906, lxxix, 251.

[4] See *v. Tappeiner, H.*, and *Jodbauer, A.*, Die sensibillisierende Wirkung fluorescierender Substanzen, Leipzig, 1907; *Flexner*, Jour. Exper. Med., 1906, viii, 1; *Mathews*, Physiological Chemistry, New York. 1917, p. 44.

[5] See *Eder*, Handb. d. Photographie, Halle a. S., 1902, vol. ii, part 2.

[6] *Finsen, N.*, Mitt. a. Finsens med. Lysinst., 1900, vol. i to x.

[7] *Burge, W. E.*, Am. Jour. Physiol., 1917, xliii, 429.

[8] For histological details see *Möller*, Bibliotheca Medica, 1900, Heft 8.

[9] *Soret*, Arch. d. sc. phys. et nat., Genève, 1878, p. 322, 359.

[10] *Kober, P. A.*, Jour. Biol. Chem., 1915, xxii, 433.

hence, the filtration of ultraviolet rays through solutions of these substances inhibits the toxic action of the rays upon living cells.[1]

The effects produced by ultraviolet light are familiar in the form of sunburn. More serious erythema and even deeper lesions are produced by exposure to naked electric arcs, especially those with magnetite poles (iron giving a spectrum rich in ultraviolet rays), to quartz mercury vapor lamps, and to other powerful illuminants which are used commercially. Fortunately, as has been stated, ultraviolet light does not penetrate well vascularized tissue for more than about 0.5 mm., and while the cornea is transparent, the lens of the eye protects the retina so that resulting burns are superficial and of little practical importance, especially as a thin layer of ordinary glass completely absorbs the ultraviolet light. The general effect of ultraviolet light on the organism is to increase metabolism and, secondarily, to stimulate the blood-forming organs and general resistance to infection; hence, notwithstanding the slight penetration of sunlight, the exposure of the bodies of tuberculous persons to direct action of the sun's rays at high altitudes has produced extraordinary improvement in the lesions, and in many cases caused rapid restoration to health.[2]

Trauma.—The various forms of mechanical injury which the body may suffer need not be considered here in detail. The significance to life and health depends upon the extent of the injury and the part of the body affected. Thus, a concussion of the brain, even without obvious structural lesion, may be immediately fatal, while extensive laceration or crushing of a limb or muscle may be readily recovered from.

Foreign Bodies.—We shall see later how the presence of lifeless foreign bodies, or of animal and vegetable parasites—bacteria, protozoa, etc.—may be harmful to the organism, and the adaptive measures by which in favorable cases protection is secured.

Poisons.—Certain forms of poisons are to be reckoned among the external agents harmful to the body. These will be considered in a later section.

Increased Atmospheric Pressure (*Caisson Disease*).[3]—An extreme increase in atmospheric pressure, such as is often nowadays maintained in tunnels, caissons, and other construction works, is sometimes the occasion of death, especially when the pressure is relieved by a too sudden return to normal conditions, that is, in what is technically called decompression. The danger seems to lie, apart from individual susceptibility, in the rapidity of the decompression.

When the pressure is relieved, susceptible individuals may breathe with difficulty, be cyanosed, and bleed from the nose, ears, eyes, and other mucous membranes. There may be pain in the joints, muscles, and abdomen. There may be paralyses, especially of the lower extremities. The bodies of the victims are often contorted from the

[1] *Harris, F. I.* and *Hoyt, H. S.*, Science, 1917, N. S. xlvi, 318.

[2] *Rollier*, La cure de soleil, Paris, 1914; *Mayer, E.*, Am. Rev. Tuberc., 1918, i, 698; 1921, v, 75; *Hyde* and *Lo Brasso*, New York Med. Jour., 1917, cv, 11.

[3] *Brooks, H.*, Proc. New York Path. Soc., 1907, vii, 58; *Boycott, Damant,* and *Haldane*, Jour. Hyg., London, 1908, viii, 342; *Keays, F. L.*, Researches of Med. Dept., Cornell Univ., New York, 1909, vol. ii; *Hill*, Caisson Sickness and the Physiology of Work in Compressed Air, London, 1912.

muscular contraction, hence the common name of the condition, "the bends." All of these symptoms may be promptly relieved by recompression. On the other hand, susceptible persons may succumb within a few hours to the disorder.[1]

The lesions in fatal cases are quite variable. During compression the blood absorbs an abnormal quantity of the gases from the air. This is due to the fact that the nitrogen is not specifically held in the blood, but dissolves in that fluid in proportion to the pressure, while the reserve oxygen capacity of the hemoglobin keeps this gas in solution. In decompression the oxygen is held but the nitrogen escapes, and to this "frothing" of the blood in too rapid decompression the symptoms and lesions of caisson disease are, in part at least, due. On external inspection no lesion may be evident; or there may be marked cyanosis of the face and mucous membranes of the mouth, nose, etc Crepitation of the skin may be elicited on light pressure, even

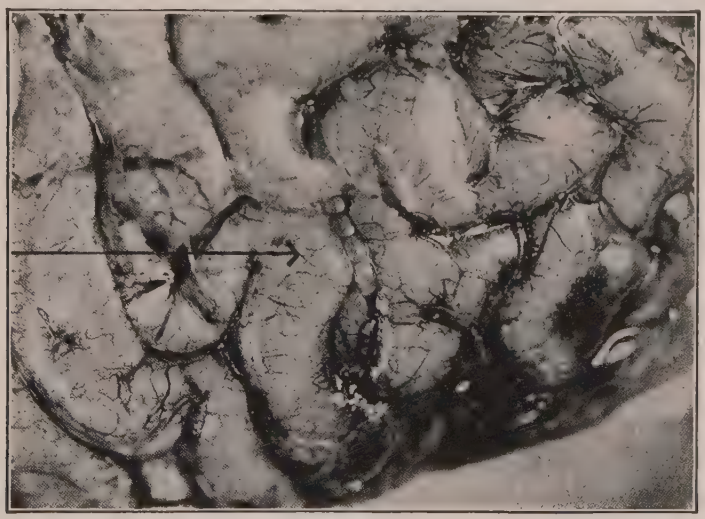

Fig. 3.—Caisson Disease.
Air in the vessels of the pia mater on the surface of the brain.

though the skin be not obviously puffed up. The internal lesions are also variable. Of these, general venous congestion and frothy blood in the veins and capillaries are the most constant and characteristic. The gas in the vessels may be best seen in the pia mater cerebralis (Fig. 3) and in the omentum. Petechial hemorrhages may be found in the brain and cord. The gas sometimes accumulates in small blebs in the nerve tissue.

In cases which recover from the primary effects of the pressure there may be secondary degenerations in the nervous system, paralysis, emaciation, trophic ulcers, etc.

Internal Conditions of Disease.

In distinction to those external agencies which lead to disease, there are many conditions of the body itself which are incompatible with the maintenance of health. There are also general conditions, due to disturbances of metabolism, such as diabetes and gout, which we shall consider separately later, in which abnormal amounts of sugar and uric acid are present, leading to many local and general disturbances.

[1] For acute effects of caisson disease, see *Erdman*, Am. Jour. Med. Sc., 1913, cxlv, 520.

The powerful influence of the emotions on the bodily functions has recently had many experimental demonstrations.[1] The relationship between excessive mental activity and some of the diseases of the nervous system, the heart, and the arteries, has long been suspected, if not proved, but there is no question as to the relationship of severe shock to the production of diabetes.

But by far the more common internal conditions associated with disease are the structural and functional alterations of the various organs of the body, which may lead directly or indirectly to the most complex departures from the normal. Some of these will be considered more in detail in later sections of this book. We may note here, however, as examples, a few of these complex relationships between local lesions and the general welfare of the organism.

Lesions of the heart valves lead to disturbances of the circulation of the blood in various parts of the body, so that, as we shall see later, both functional and structural changes harmful to the individual may occur in important viscera, for example, in the lungs, kidneys, liver, blood-vessels, etc., and secondarily in the walls of the heart itself.

In the gastrointestinal canal defective innervation, or trauma, or tumors, or constrictions may lead to the accumulation of ingested material, to innutrition, to intoxication through decomposition of the albuminous or other ingredients of the retained material.

So in the liver, an insufficient production of bile or an occlusion of the gall-ducts may lead to digestive disturbances, to a deposition of bile pigment in various parts of the body—icterus; to the accumulation of bile in the blood—cholemia. On the other hand, an overproduction of bile may take place in the destruction of abnormal quantities of red blood-cells, leading to icterus.[2] Furthermore, through disturbances in the glycogenic function of the liver, sugar may accumulate in the blood.

These examples of the bearing of functional disturbances and structural lesions of individual organs upon each other, and upon the welfare of the body as a whole, must suffice, since the scope of this book does not permit us to enter upon this wide field of pathological physiology, for the adequate consideration of which we must refer to systematic treatises on the practice of medicine.

Race.—Examples of racial disposition to disease are not uncommon. Thus African negroes are less susceptible than are the whites to malaria. On the other hand, in this country the negro is especially vulnerable to tuberculosis.

Age is an important factor in the liability to disease, though the reason for this is in very few instances at all clear. In childhood, for example, diseases of the digestive system are readily induced by unsuitable food. In advanced life, the vascular system is a vulnerable part of the body. This apparent predisposition of age may, however, be referred to the wearing out of the vascular mechanism.

Sex appears to be a definite factor in disease disposition, for such

[1] *Cannon*, Bodily Changes in Pain, Hunger, Fear, and Rage, New York, 1915.
[2] *Hooper, C. W.*, and *Whipple, G. H.*, Jour. Exper. Med., 1916, xxiii, 137.

maladies as diabetes, gout, general paralysis, tabes, etc., are more common in males than in females. But here, as in the age factor, many obvious external conditions, such as occupation, food, excesses in food and drink, syphilis, etc., may be invoked as elements of determining importance but not inherent in the condition of sex. The conditions incident to child-bearing, however, favor the occurrence of many more or less serious abnormalities of structure and function peculiar to the female.

Heredity.—The relations of heredity to disease are extremely complex and subtle, and our knowledge of the subject is still too meager to permit of a profitable exposition within the limits which this book imposes. In certain infectious diseases, syphilis, for example, the infective agent may be transmitted from the parents to the offspring. This, however, is not the conveyance of physiological or structural peculiarities, but only of an external disease excitant.

For the sake of clearness of thought and correctness of observation it is well for the student and physician to remember that those features and capacities of the organism which are inherited, are those and those alone derived from the maternal and paternal germ plasm, or through the reaction of these upon each other. The many and varied external influences brought to bear upon the fetus during intrauterine life, may induce marked departures from the normal, but these abnormalities are not in a proper sense inherited. They are more correctly designated congenital.[1] A curious example of such external influence is the production of monsters occasionally delivered after exposure of the pregnant uterus to large amounts of *x*-ray with therapeutic intent, such as the reduction in size of a fibromyoma.

Susceptibility to disease may be inherited, to tuberculosis, for example; though we are unable to define clearly either structural or functional traits to which this vulnerability may be attributed.

There are numerous examples of hereditary anomalies or dispositions to disease. We cannot consider them here in detail, but we may mention as examples, hemophilia, color-blindness, nyctalopia, myopia, neuroses of various types, angioneurotic edema,[2] obesity, gout, and diabetes.[3] The inheritance of a chemical anomaly is seen in the cystinurics[4] and alkaptonurics.

[1] Many interesting examples of heredity in man have been collected by *Bateson, W.*, Mendel's Principles of Heredity, Cambridge, 1913; and by *Davenport, C. E.*, Heredity in Relation to Eugenics, New York, 1911. See, also, *Morgan, T. H.*, Heredity and Sex, New York, 1913; and *Castle, W. E.*, Heredity, New York, 1913. For an interesting study of Mendelian heredity, as exemplified in a crossing between the white and black races, see *Fischer, E.*, Die Rehobother Bastards, Jena, 1913.

[2] *Crowder* and *Crowder*, Arch. Int. Med., 1917, xx, 840.

[3] For a full discussion of these anomalies, see *Pearson, K.*, Treasury of Human Inheritance, Galton Eugenics Laboratory, London, 1912.

[4] *Garrod, A. E.*, Inborn Errors of Metabolism, London, 1909. For a fuller exposition of the subjects considered in this chapter, consult *Adami, J. G.*, Principles of Pathology, vol. i, Philadelphia, 1908; *Thoma, R.*, Lehrb. d. pathologischen Anatomie, Stuttgart, 1894; *Bouchard, Ch.*, and *Roger, G. H.*, Pathologie générale, Paris, 1912–14.

CHAPTER II.

CHANGES IN THE CIRCULATION OF THE BLOOD.

General Conditions.

The circulation of the blood in the body is maintained by a very efficient and delicate mechanism capable of prompt and effective adjustment to changes in the local and general conditions under which the body is placed.

The factors especially concerned in the maintenance of the normal circulation and in its adaptability to new and unfavorable conditions are the contractile heart with its valves, the elastic arteries, the innervation of the heart and vessels, gravitation, and the various phases of pressure and suction upon the veins from external sources, direct muscular action, respiratory movements, etc., which promote the passage of the blood upon its rounds. Finally, the character of the blood itself may have an important bearing upon the efficiency of the circulatory mechanism. Alterations in any of these factors may involve disturbances of the circulation.[1]

We may glance briefly at some of these factors in the circulation, and first at *the heart itself*. The energy sustaining the circulation is primarily derived from the contractile heart, so that the condition of its muscle and innervation are of the first significance. Should the heart muscle be enfeebled, through lack of proper nutriment or innervation or by degeneration of the muscle, for example, the circulation suffers in manner and degree depending upon the part of the heart involved. Thus if the muscle of the right ventricle is enfeebled, blood is not properly drawn into the ventricle and is not sent with sufficient force into the lungs. The venous system then becomes overfilled with blood. If the muscle of the left ventricle be enfeebled, too little blood is sent into the arterial system and the pulmonary vessels are not properly emptied.

Changes in *the valvular openings of the heart* or in the valves themselves lead to disturbances of the circulation. Thus if the openings are narrowed, too little blood passes them; or if the valves fail to close properly, some of the blood flows backward through them. In this way both the pulmonary and the systemic veins become overfilled.

The circulation may also suffer through alterations in *the walls of the blood-vessels*. The elasticity and contractility of the arterial walls are important factors in the maintenance of a normal circulation, since they sustain and reinforce the heart pressure on the blood and convert the pulsating movement imparted by that organ into a continuous, uniform flow through the capillaries and veins. If the arterial walls become stiffened and less elastic, or if their lumen becomes narrowed,

[1] See, for details concerning the physiology and pathology of the circulation, *Wiggers*, Circulation in Health and Disease, Philadelphia, 1915 (bibl.).

more work is thrown upon the heart muscle. Thus the peripheral circulation is impaired unless, in a manner which we shall presently consider, the power of the heart muscle is increased by hypertrophy. Obstruction of the veins may induce similar disturbances in the heart and an impaired local or general circulation.

The circulation of the blood being controlled by *the nervous system* through the distribution of nerves to both the heart and the vessels, alterations in the central nervous system affecting the vagus or the sympatheticus, or severe traumatic injuries to the body involving reflex disturbances, may induce serious local or general interference with the circulation of the blood.

The *respiratory movements* of expiration and inspiration favor the circulation of the blood, so that interference with these may be of considerable importance. Thus pleuritic effusions, severe spasms of coughing, etc., may induce changes in the pulmonary circulation and the right heart as well as in the systemic circulation.

The movements of *the muscles* of the trunk and extremities acting together with the valves of the veins contribute to the forces carrying the blood forward in circulation. Severe spasm of the muscle, as in epilepsy, tetanus, strychnine poisoning, etc., may induce stagnation of the blood in the veins of the trunk and the viscera so that it does not return properly to the heart.

These are some of the more important of the changes which the general circulation suffers in conditions which interfere with the circulatory mechanism.

The means by which the heart and the blood-vessels adapt themselves to various disturbing conditions through compensatory alterations will be considered in the chapters in "Special Pathology" dealing with these organs.

We shall now consider in more detail the local effects of a disturbed circulation.

Hyperemia and Anemia.

Within physiological limits the amount of blood in a part may vary considerably under vasomotor control according to the functional necessities of the part or vascular territory. Under a great variety of abnormal conditions the blood content suffers changes so excessive and so lasting as to be pathological. It is the latter alone which we are to consider here.

A part of the body may contain an excess of blood, a condition called *hyperemia* (congestion). This is distinguished from *plethora*, which signifies a general excess of blood in the body. On the other hand, there may be too little blood in a part of the body, a condition which is called *anemia*.

HYPEREMIA.

Hyperemia may occur either through increased arterial supply, *active hyperemia* (acute congestion), or through some hindrance to the venous outflow of the part, *passive hyperemia* (venous congestion).

Active Hyperemia.—This may occur through dilatation of the arteries by the action of various physical and chemical agents directly upon their muscular coats, or through the vasomotor nerves, or from the reduction of pressure upon the vessels from without.

Thus, injuries or stimulation of the vasomotor nerves, heat, the sudden evacuation of large exudates, trauma, and the action on the vessels of a great variety of chemical irritants may lead to a dilatation

Fig. 4.—Hyperemia of the Blood-vessels near a Bronchus. In chronic bronchitis.

of the vessels, and, as friction is diminished with the dilatation of the lumen, to a more rapid flow of the blood.

Under these conditions the affected region becomes redder, warmer, and may be more or less swollen, and under certain conditions the arterial characters of the blood and pulsation of the vessels may be extended into the venous trunks.

Passive Hyperemia (venous congestion).—In passive hyperemia due to obstruction to the outflow of blood from a part, there is an overfilling of the veins and capillaries (Fig. 4). The hindrance to the

outflow of blood may be due to compression of the vessels from without, as from tumor, aneurysm, ligature, displacement, or from new interstitial tissues in various organs. It is frequently the result of thrombosis.

One of the most fruitful determining causes of passive hyperemia is the lesions of the heart which interfere with the regular entrance and exit of the blood from that organ. Thus, in incompetence or stenosis of the mitral valve the pulmonary vessels become congested; the right ventricle does not properly empty itself. So the systemic veins in varying degrees suffer engorgement, and the viscera become involved in the secondary alterations due to chronic hyperemia.

The effect of venous obstruction varies greatly, depending upon its degree, upon the rapidity of its occurrence, and upon the structure and functional importance of the part involved. If, as in most instances is the case, venous anastomoses exist between the partially or wholly

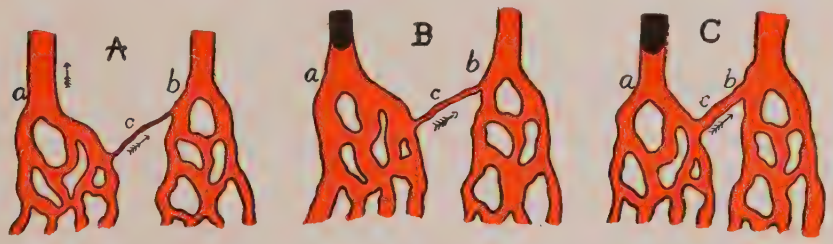

FIG. 5.—DIAGRAM ILLUSTRATING THE ESTABLISHMENT OF COLLATERAL CIRCULATION IN OBSTRUCTION OF A VEIN—AFTER RIBBERT.

The veins *a* and *b* at *A* are connected by a slender trunk, *c*. If *a* in *B* is occluded, as by a thrombus, the blood cannot all pass out of the territory drained by *a*, so that the vessels here are dilated—congestion. If, however, the small anastomosing trunk widens as at *C*, the congestion is relieved by the conveyance away of the blood through the vein *b*.

occluded and other vessels, these may enlarge, and with the establishment of this *collateral circulation* a more or less complete adaptation to the changed conditions is secured (see Fig. 5). The collateral veins and even capillaries in the involved region widen and their walls thicken; and thus while for a time hyperemia of varying intensity may exist, this gradually resolves.

The possibilities of adaptation to venous obstruction are sometimes very great even when large trunks are concerned. Thus, a ligature of the femoral vein or a blocking of the inferior or superior vena cava may be compensated by the establishment of abundant collateral channels. On the other hand, after the blocking of the renal or splenic or of a main trunk of the portal vein, the circulation is re-established with difficulty.

If a collateral circulation be not at once and readily established, and often even if this be the case, local venous obstruction leads to certain well-defined changes in the hyperemic region. If the obstruction be partial, the flow of blood is slower than normal; the vessels are dilated; more or less fluid may transude into the surrounding tissues; and diapedesis (see page 106) of the red blood-cells may occur. On the other hand, if the obstruction be complete in a large venous trunk, the capillaries and veins in the involved region dilate; the axial stream of ery-

throcytes in the veins disappears; the entire lumen is crowded with them; the blood pressure rises; the current wavers, slows, and stops. Then the red cells become packed into a homogeneous mass in the dilated vessel—this is *stasis*. Diapedesis and transudation now occur in the capillaries and veins of the involved region. Finally, if the circulation be not re-established, hemorrhagic infarction (see page 40) or death of the tissue—necrosis—may follow.

If the venous obstruction be removed, as may be done experimentally in the tongue or mesentery of the frog (see page 131), one may observe under the microscope the disappearance of the stasis and the re-establishment of the circulation. The homogeneous blood mass resolves itself into its component corpuscles; the blood moves at first fitfully and irregularly, then the current is established; the distention diminishes, and, after a longer or shorter time, if the lesion have not been too extreme, the part assumes its normal appearance.

In passive hyperemia the tissue involved is more or less dark red in color—*cyanotic*—owing to the accumulation in the vessels of unaerated blood; the temperature may be lowered when the area concerned is extensive; it may also be swollen in part from the distention of the vessels, in part from the extravasation of fluid; finally, there may be pulsation and increased pressure in the veins.

If the hyperemic condition be long continued—*chronic congestion*—the walls of the involved vessels may become thickened; there may be interstitial fibrous hyperplasia in the affected region; or there may be varying degrees of cell degeneration or of atrophy. Thus function may be interfered with or suspended.

In many instances of diminished heart power or when for any reason the blood circulates with difficulty under favorable conditions, the effect of gravity may manifest itself in dependent portions of the body or of the organs, so that these become hyperemic. This condition is called *hypostatic congestion*. The most marked example of this condition is in the lungs of debilitated persons, the dependent portions of which frequently become engorged with blood. This is often associated with edema, atelectasis, and more or less cellular exudate in the air spaces.

ANEMIA.

The word anemia is used not only to denote the lack of blood in a part, but also to indicate a reduction or alteration in various constituents of the blood itself, a condition familiarly called "poverty" of the blood. General anemia due to impoverishment of the blood will be considered in the chapter on the Special Pathology of the Blood and the Blood-forming Organs. We are here concerned only with *local anemia*—ischemia.

Local anemia may be due to the cutting off of the blood supply by the occlusion of the arteries in thrombosis and embolism; by ligatures; by the narrowing of the lumen through pathological processes in the wall of the vessel; by tumors, exudates, etc.; by contraction of the vessels from nerve lesions as in Raynaud's disease; by the action upon the

vessel of physical agents—cold—or by chemical substances or drugs which induce marked constriction—suprarenal extract and ergot. Furthermore, mechanical pressure upon the vessel from without or compression of an entire organ or part may induce various grades of anemia.

The affected part or organ in anemia becomes paler than normal, often with a yellowish tinge; the temperature is lowered; and the volume may be diminished; finally, if the absence of blood persist, the function and nutrition of the involved part suffer, and atrophy, fatty degeneration, and death of tissue may occur.

If, however, the anemia be only partial or if it be of short duration, in some organs the nutrition may not suffer in marked degree; in others, however, the brain, for example, extreme damage may follow even a temporary anemia.

The degree, duration, and results of local anemia are largely dependent upon the cause of the shutting off of the blood supply, and the possibility of its restoration directly or through the establishment of a collateral circulation. Thus, for example, anemia from compression as from an arterial ligature may at once resolve if the determining cause be removed. But even though an artery remain blocked, circulation may be in a measure restored by the dilatation of anastomosing capillaries or by the backflow of venous blood into the region deprived of its vascular pressure from the closed arteries. While a certain amount of fresh blood may reach the affected region in these ways, it is only when anastomoses exist between the branches of the closed and neighboring arterial trunks that a fairly complete collateral circulation can be established. For a further consideration of this subject see Embolism (page 39).

Hemorrhage and Transudation.

HEMORRHAGE.

Hemorrhage is an escape of blood from the heart or vessels. It may occur from a rupture of the walls of the vessels, and is then called hemorrhage by *rhexis*. The rupture may be occasioned by injury, by lesions of the walls of the vessels which render them too weak to resist the blood pressure from within, or it may occur from the blood pressure in the thin and incompletely developed walls of new-formed vessels as in granulation tissue, tumors, etc. The arrest of hemorrhage may take place through the contraction of the wall of the vessel or by the formation of a clot.

Under other conditions, without recognizable changes in the vessels, all the elements of the blood may become extravasated by passing, without rupture, through their walls. This is called hemorrhage by *diapedesis*. Such hemorrhages are usually small, but may be very extensive. They occur in the smaller veins and capillaries, the cells and fluids of the blood passing out through the cement substance between the endothelial cells. Although no marked morphological changes have as yet been detected which explain this extravasation, it is probable that some change in the nutrition of the walls does occur which renders them more

permeable. Hemorrhage by diapedesis is apt to occur as a result of venous congestion, or when the flow of blood in the smaller vessels has been suspended for some time; or it may result from the action of some poison, or from an injury not leading to rupture; or it may occur in incompletely developed blood-vessels in tumors and other new-formed tissues.

In the extravasation of blood by diapedesis the white blood-cells may pass through the walls of the vessels, partly at least in virtue of their ameboid movements; the red cells, on the other hand, having no power of spontaneous movement, are, according to Arnold, carried passively through the walls by minute currents of fluid which, under the changed condition, stream in increased force and volume through the endothelial cement substance into the tissue spaces outside.

The altered condition of the blood-vessels leading to hemorrhage may be local or general, and in the latter case it may either be congenital, as in some cases of the hemorrhagic diathesis, or it may be the result of a general disease, such as scurvy, purpura, etc. The presence of bacteria in the vessels, or of bacterial or other poisons in the blood, as in malignant endocarditis and in hemophilia neonatorum, may induce changes in the walls of the vessels, leading to extravasation.

Forms of Hemorrhage.—Very small hemorrhages are called *petechiæ*, larger, diffuse accumulations of blood in the interstices of the tissues are commonly called *ecchymoses* or *suggillations*. A complete infiltration of a circumscribed portion of tissue with blood is called a *hemorrhagic infarction*. A collection of blood in a tumor-like mass is called a *hematoma*. Special names are given to hemorrhage in different parts of the body; thus, bleeding in the lungs is called *hemoptysis;* vomiting blood from the stomach, *hematemesis;* nosebleed, *epistaxis;* hemorrhage from the uterus, *metrorrhagia;* certain forms of brain hemorrhage, *apoplexy*. In the so-called *hematuria* the blood may be derived from either the kidney or the bladder. Sometimes the elements of the tissue into which the blood escapes are simply crowded apart; sometimes, as in the brain, they are broken down.

The extravasated blood in the tissues usually soon coagulates, although exceptionally it remains fluid for a long time. A certain number of the white blood-cells may wander into adjacent lymph-vessels, or they may remain entangled with the red cells in the meshes of the fibrin. The fluid is usually soon absorbed; the fibrin and a portion of the white blood-cells disintegrate and are absorbed (see page 75). The red blood-cells soon give up their hemoglobin, which decomposes and may be carried away or be deposited either in cells or in the intercellular substance at or near the seat of the hemorrhage, either in the form of yellow or brown granules or as crystals of hematoidin (see page 68). Sometimes all trace of extravasations of blood in the tissues disappears, but frequently their seat is indicated for a long time by a greater or less amount of pigment or by new-formed connective tissue. Occasionally the blood mass, in a more or less degenerated condition, becomes encapsulated by connective tissue, forming a cyst.

The action of phagocytes (see page 119) in the disposal of dead ma-

terial is here, as it is under a great variety of conditions, an important factor in the restoration of the body, after lesion, to its normal conditions.

Hemorrhages in the New-born.

Hemorrhages, sometimes extensive, in various parts of the body—gastrointestinal canal, mouth, nose, navel, or the viscera—are not infrequent in the first few days of life. Aside from the occasional discovery of ulcers in the gastrointestinal walls, the reason for these hemorrhages is not evident at autopsy.[1] This condition has been called morbus maculosus neonatorum. Hemorrhages from the skin, mucous membranes, or navel may take place in the syphilitic new-born. Hemoglobinuria may occur in epidemic form in young children.

Hemophilia (*Hemorrhagic Diathesis*).

This abnormal condition consists in a liability to persistent hemorrhage on the slightest provocation, and is dependent upon some constitutional peculiarity which is unknown to us. It is usually hereditary, being transmitted only through the female line and manifested in the males; it appears in females only when the parents are a hemophilious male and a female carrying hemophilia. The condition is, therefore, sex-limited.[2] An uncommon thinness of the intima of the arteries has been noticed in some cases of "bleeders," and other changes have been described; but there are no constant lesions associated with the hemorrhages, as yet discovered, which would satisfactorily account for their occurrence. The hemorrhages may be traumatic in origin, or they may occur spontaneously from the mucous membranes.

TRANSUDATION.

Transudation is the passage, through the walls of the blood-vessels into the interstitial spaces outside, of fluid from the blood, with little or no admixture of its cellular elements. This occurs constantly, to a certain extent, under normal conditions, and forms the commencement of the lymph circulation. But when the amount of fluid passing through the walls of the blood-vessels is increased, or its outflow into the larger lymph-trunks is hindered so that it accumulates in undue quantity in the interstices and lymph-channels of the tissues, the condition is pathological.[3]

An accumulation of transuded fluid in the interstices of the tissues is called *edema;* in the serous cavities, *dropsy.* Extensive edematous infiltration of the subcutaneous tissue is called *anasarca.* If the transudate accumulates in the pleural cavity the condition is called *hydrothorax;* in the pericardium, *hydropericardium;* in the ventricles of the brain, *hydrocephalus.* In similar fashion various other names are in

[1] For a study of hemorrhagic diseases of the new-born, with bibl., see *Graham*, Jour. Exper. Med., 1912, xv, 307.

[2] For a discussion of this and other anomalies of heredity, see, *Pearson, K.*, Treasury of Human Inheritance, London, 1912.

[3] For a study of edema see *Meltzer*, Harrington Lectures, Univ. of Buffalo, Am. Med., 1904, viii, 19; also *Pearce*, Arch. Int. Med., 1909, iii, 422.

common use for the accumulation of transudates in the body cavities; as *hydroperitoneum* (ascites), *hydrarthrosis*, *hydrocele*, etc.

Its occurrence may depend upon some hindrance to the venous circulation or increase of capillary pressure, especially when associated with alterations in the walls of the blood-vessels, or upon changes in osmotic pressure induced by a reduction in the nutrient efficiency of the blood, by injuries, or in other ways which may affect the processes of filtration and osmosis, by which chiefly, it is believed, the normal transudation of fluids occurs. There is, furthermore, strong and increasing evidence that the endothelial cells of the capillaries possess active secretory or other functional capacities which should be taken account of in the attempt to comprehend transudation as well as many other pathological phenomena and lesions. A simple interference with the outflow of lymph does not usually alone suffice to induce transudation, although it may favor its occurrence. Edema may depend upon little understood abnormalities of the nervous system, as in the so-called neuropathic edemas.

In addition, Widal and his pupils[1] have called attention to the nature of the edema in chronic nephritis due to the retention of sodium chloride by the excretory failure of the kidneys. This type of edema is apparently caused by the necessity for a fixed chloride content of the blood, so that when chloride is retained water is retained also in the interstices of the tissues. If dropsical patients are put for a few days upon a salt-free diet, they may lose large quantities of water, even as much as fifteen kilos; but if after this period ten grammes of salt are added to the diet, edema, with re-accumulation of water, occurs.

The transuded fluid, called *transudate*, is usually transparent and colorless or yellowish; it contains the same salts as the blood plasma, but less albumin. It may contain fat, mucin, urea, biliary acids, coloring-matter of the bile; fibrinogen is usually present in variable quantity, and, rarely, fibrin. It may contain endothelial cells from the lymph-spaces or lining cells from the serous cavities, and a variable number of red and white blood-cells. The amount of fluid which may accumulate in the tissue varies greatly, depending upon whether they are loose or dense in texture. The fibers and cells of loose tissues may be crowded widely apart; the cells are apt to be more granular than normal, they may contain droplets of fluid, or they may be atrophied. Transudates occurring in inflammation usually contain a considerable number of white blood-cells and more or less fibrin, and differ in this from the non-inflammatory transudations; but in some cases there is no sharp distinction between them. The inflammatory transudates are often called exudations or *exudates*.

Resorption and Absorption.

Under many conditions, both normal and abnormal, fluids and solid particles are taken into the recesses of the tissues from without, or are gathered from one place in the tissues to be carried in the blood or lymph-currents or by cells to other parts or to places of excretion. Thus

[1] *Widal, Ambard,* and *Weill,* Sem. méd., 1913, xxxiii, 370.

from the intestinal contents both liquid substances and small solid particles, such as fat droplets, bacteria, etc., may be taken into the body fluids. In exudative inflammations, such as pleurisy or pneumonia, large quantities of fibrin, red and white blood-cells, and fluids may accumulate in the cavities, to be presently removed. So also dead tissue, blood clots, etc., and foreign bodies may be removed through various processes of resorption.

The absorption of fluid substances or the resorption of those which are rendered soluble takes place through the lymph-channels, as we have seen, whence they may be eliminated through the excretory organs. Solid material, such as fibrin, dead cells, etc., may be removed either through the action of fluids which render them soluble, lytic fluids (page 126), or through the intervention of living cells, phagocytes (page 119). These processes will be considered in detail in a later section of this book.

Thrombosis and Embolism.

THROMBOSIS.

Thrombosis is the coagulation of the blood or the agglomeration or agglutination of the formed elements of the blood into a more or less coherent mass during life. The coagulum or mass is called a *thrombus* (Fig. 6).

Thrombi may be composed of fibrin and of red and white blood-cells intermingled in about the same proportion as in an ordinary extravascular blood clot (Fig. 7). These are called *red thrombi* and usually occur from some sudden stoppage of the circulation. Other thrombi, usually such as form while the blood is in motion, may consist almost entirely of white blood-cells with a little fibrin, or of these intermingled with blood-platelets; or they may consist almost entirely of blood-platelets; all of these forms are called *white thrombi*. Red thrombi, when decolorized by changes in the blood pigment, may somewhat resemble genuine white thrombi. *Mixed thrombi* are usually lamellated (Fig. 8) and contain varying proportions of fibrin, red and white blood-cells, and platelets. The fibrin fibrils in thrombi, as elsewhere, often coalesce, forming hyaline masses. A similar change may take place in the blood-platelets. Thrombi may consist almost wholly of red blood-cells.

FIG. 6.—OCCLUDING THROMBUS OF THE ILIAC.
The vessel is laid open, showing the lamellated clot.

Causes of Thrombosis.—Thrombi may occur as the result of an injury to the wall of

a vessel, or may follow its compression or dilatation; they may result from some alteration of the wall of the vessel by disease, or by the retardation of the circulation as is well shown by the fact that thrombi are three times as frequent in the veins as in the arteries. So long as the endothelial lining of the vessel is intact, simple retardation of the circulation does not usually alone suffice to induce coagulation; but changes in the endothelium in a great variety of conditions, such as inflammation, degeneration, atheroma, calcification, and the presence of bacteria or their toxins, tumors, and foreign bodies, favor its occurrence, especially when associated with changes in the circulation or in the character and contents of the blood. Thrombi may develop from an embolus. Thrombosis is a not infrequent complication of the infectious diseases as well as of the cachectic conditions associated with various acute and chronic general diseases.

One may conveniently class the various determining causes of thrombosis into: 1, those associated with a slowing of the blood-current; 2, those relating to changes in the walls of the blood-channels; and 3, those involving such alterations in the blood itself as favor coagulation. These factors are frequently associated.[1]

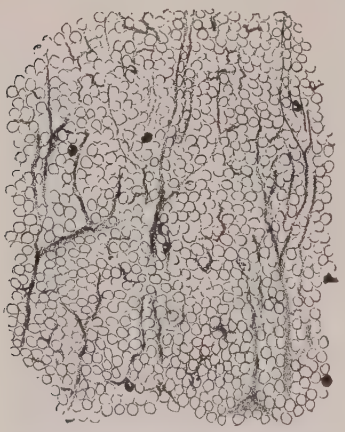

Fig. 7.—Portion of Red Thrombus. This shows red blood-cells, fibrin, and a few leucocytes.

1. Disturbances of the circulation favoring thrombosis are frequently dependent upon enfeebled heart action, and thrombi may then form in the auricles behind the valves or among the trabeculæ of the heart (Fig. 7), behind the valves of the veins, in the veins of the lower extremities, in the great venous sinuses of the brain, or wherever by reason of abnormal conditions the regular flow of the blood is interfered with—as in aneurysms, varices, etc. Such thrombi are sometimes called *stagnation thrombi*. When forming under marked asthenic conditions they are called *marantic thrombi*. In this class belong thrombi induced by pressure or ligature of the vessels.

2. Thrombi associated with alterations in the walls of the blood-vessels may follow mechanical injuries to the vessels and may be conservative in the control of hemorrhage. The action of various forms of pathogenic bacteria within or in the vicinity of blood-vessels inducing lesions of the walls is a fruitful determining factor in thrombosis. This is common in acute endocarditis, in septicemia, in various forms of phlebitis, and in tuberculosis. In chronic lesions of the walls of the heart and blood-vessels, associated with degeneration and necrosis (atheroma, calcification, etc.), thrombi may form. The growth of tumors into the blood-channels affords favorable conditions for the development of thrombi.

[1] For a study of the conditions relating to the occurrence of thrombosis, such as changes in the coagulability of the blood, power of agglutination, local and general condition of the blood flow, and endothelial damage, see *Aschoff*, Cartwright Lecture, Arch. Int. Med., 1913, xii, 503. For full review, see, also, *Hanser, R.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1921, xix², 147 (bibl.).

3. The alterations of the blood itself favoring thrombosis are obscure. Such are the impoverishment of the blood in anemia, the presence of bacterial toxins or of the bacteria themselves in various infectious diseases. Many of the so-called marantic thrombi are probably due to the presence of bacteria or of their toxins in the blood or in the walls of the vessels. Some cases of "white swelling" following parturition are probably of this nature.

Among the less frequent alterations of the blood favoring thrombosis may be mentioned the presence of hemolytic substances, as in the transfusion of alien blood and the artificial introduction of certain animal and vegetable extracts.

Forms of Thrombi.—Various forms of thrombi, aside from those already described, have received special names. Thus thrombi are called *primary* or *propagated*, depending upon whether they are con-

Fig 8.—Lamellated Thrombus.

This is an occluding thrombus. At the right and also above are masses of red blood-cells, while the remainder is largely fibrin in layers, indicating successive deposits.

fined to the original site of formation or extend for some distance from the point of origin. Sometimes such extension is marked by variations in the color, density, and structure of the extending thrombus. A *secondary thrombus* is one formed upon an embolus or a pre-existent thrombus. A thrombus may be *obstructing* or *parietal; solid* or *canalized; simple* or *infective;* it may be *arterial* or *venous*—all names whose significance is obvious.

Agglutinative Thrombi.[1]—The recent studies on agglutination and hemolysis (page 203) have led to the belief that certain thrombi occur-

[1] Consult *Flexner*, Jour. Med. Research, 1902, N. S. iii, 316: *Pearce, R. M., ibid.*, 1904, N. S. vii, 329; and *Pearce* and *Winne*, Am. Jour. Med. Sc., 1904, cxxviii, 669 (bibl.).

ring in infectious diseases, as well as under other conditions, may arise from the development of agglutinative substances in the blood. Under the action of these substances the red blood-cells may, without the formation of fibrin, clump together, leading to thrombosis. Such thrombi are called agglutinative thrombi. They have been observed repeatedly in typhoid fever and other infections. In such masses of agglutinated red blood-cells the individual corpuscles may not be seen, the whole presenting a hyaline mass. Thus may be formed a variety of the so-called hyaline thrombi. Welch[1] has suggested the probability that under similar conditions leucocytes also may form agglutinative thrombi.

Hyaline Thrombi.—Under a variety of conditions, but especially in local and general infections and in intoxications, there is present in the capillaries and in the small arteries and veins a homogeneous, translucent, nearly colorless material, partially or wholly blocking the vessels. This hyaline material, whose origin is still in doubt, has in some instances a staining reaction similar to fibrin. In other cases hyaline thrombi are probably special forms of agglutinative thrombi (see above).

Alterations in Thrombi.—After a certain amount of shrinkage by which the fluids are squeezed out and the thrombus becomes denser and drier, the changes which occur in it may be in the direction either of degeneration and absorption or of organization. The leucocytes, the fibrin, and the blood-plates may degenerate, forming a granular material which may become infiltrated with salts of lime, forming the so-called *phleboliths*, or *vein stones*. In other cases the thrombi may soften and disintegrate. This softening may be *simple* and the result of fatty or other form of tissue degeneration, resulting in a white or reddish or brown grumous mass, which may resemble, but is not, pus. Or, in many instances, softening probably occurs through the autolytic processes (page 126) initiated and sustained largely by leucocytes. On the other hand, softening of the thrombus may be associated with bacteria or other infectious material with general suppuration. In this "purulent" or "septic" softening of the thrombus the risk is great of a distribution of the infectious material through the circulation. Finally, the thrombus may be replaced by a new formation of vascular connective tissue, itself disappearing by autolysis or phagocytosis as the new tissue is formed. This is called "organization of the thrombus," but in reality the new connective tissue is produced, not from the cells of the thrombus itself, but from the cells of the walls of the affected trunk, from whose vessels the new blood-vessels of the thrombus also arise (compare page 93). In this way the vessel may be completely and permanently occluded, or, more rarely, one or several channels may be established through the new connective-tissue mass (Fig. 9).

Effects of Thrombosis.—The consequences of thrombosis vary greatly, depending upon the seat, size, and nature of the thrombus. They are of two classes: 1, those depending upon the direct disturbance of circulation from the occlusion of the lumen of the vessel; and, 2, those determined by the detachment of the thrombus or the separation of

[1] *Welch*, Huxley Lecture, Medical News, 1902, lxxxi, 721.

a part of it, and the distribution of these through the circulatory channels to various parts of the body.

1. The occlusion of either arteries or veins may be compensated by the establishment of collateral circulation. The partial or total occlusion of an artery by a thrombus may lead to local anemia, degeneration, necrosis, or infarction (see page 41). The obstruction of a vein may lead to venous congestion and edema, and to various alterations already considered under the heading of Hyperemia.

For a further consideration of thrombosis of the heart and separate vessels see sections dealing with these organs in Special Pathology.

2. Whole thrombi or portions of these may be detached and carried forward by the blood-current, or, as the result of softening and disinte-

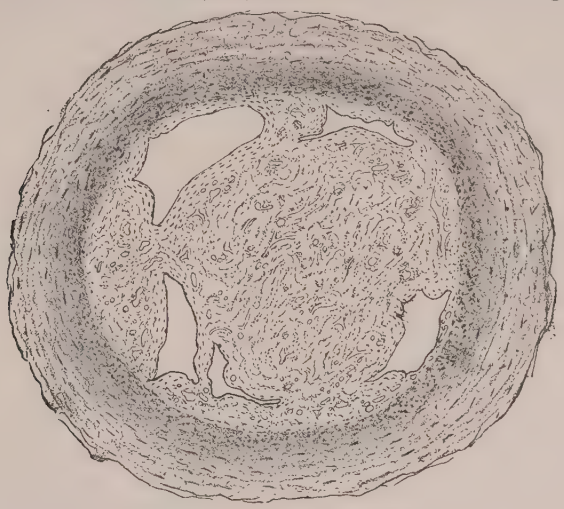

FIG. 9.—ORGANIZED THROMBUS.

This shows the vascular connective tissue which has replaced the clot, with five new channels through which the circulation is re-established.

gration, detritus, bacteria, etc., may be set free by unusual movement, by pressure, or without obvious special force.

The performances and effects of such detached portions of thrombi will be considered in the next section, under embolism.[1]

THROMBOSIS OF LYMPH-VESSELS.

Thrombosis of the lymph-vessels is of occasional occurrence. The thrombus consists of fibrin and leucocytes. It may present forms and induce changes in the lymph-channels analogous with the forms and effects of thrombi in the blood-vessels.

EMBOLISM.

Embolism is the obstruction of a blood-vessel by the arrest in its lumen of some material carried along in the circulating blood. The mass causing the stoppage is called an *embolus* (Fig. 10). This may

[1] For a thorough and admirable consideration of the subject of thrombosis and embolism, with bibliography, consult *Welch*, Allbutt's System of Medicine, 1909, vi, pp. 691, *et seq.*

be composed of a great variety of substances. The most common emboli are detached portions of thrombi, especially from the heart valves, and these may have all the variety of structure which thrombi present. Masses of bacteria or other animal or vegetable parasites, fragments of the heart valves and of tumors, droplets of fat from the medulla of fractured bones (Fig. 11), parenchyma cells,[1] masses of pigment, bubbles of air, etc., may form emboli. Embolism is, in a majority of cases, confined to the arteries and to the branches of the portal vein. Emboli after lodgment sometimes give rise to thrombosis, which may be very extensive.

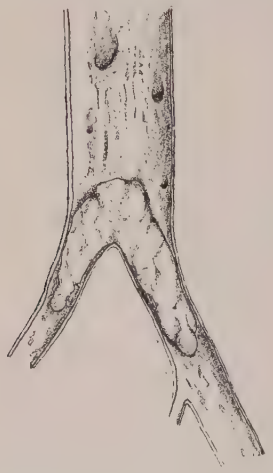

FIG. 10.—AN EMBOLUS LODGED AT THE POINT OF DIVISION OF AN ARTERY.

This is a portion of clot which has been detached from a point above and swept along the blood current. It has increased in length by coagulation at its free extremities.

Effects of Embolism—Infarction.—The changes which follow the more or less sudden and complete cutting off of the arterial blood from a part of the body by the lodgment of an embolus are so variable, depending upon the part of the body affected, the character of its vascular arrangement, and the possibilities of a collateral blood supply, that a concise comprehensive description is difficult.

When the arterial blood-current is cut off from the affected area, this does not at once become bloodless, because its vessels still contain the residual blood and a certain amount may enter at least the periphery through adjacent capillaries and small veins. Then if the involved region is not too large and the plugged vessels have sufficient anastomoses, the establishment of a collateral circulation may after a time be effected. On the other hand, if the plugged artery does not possess anastomosing trunks or is inadequately supplied with these—that is, belongs to those vessels which are called *terminal arteries—end arteries*—the effects are more marked and lasting. There is stasis in the vessels; diapedesis of the red blood-cells may occur; and while a small amount of blood may enter the periphery of the involved region through the capillaries and veins so that the vessels here may be markedly congested, the tissues are not sufficiently nourished and they suffer varying degrees of degeneration; they may die and the whole central region become necrotic. This gradually developing process is called *infarction*, and the portion of involved tissue is called an *infarct* (Fig. 12). The area of infarction corresponding to the region supplied by the occluded vessel is usually more or less wedge-shaped.

Infarcts in which the vessels are distended with blood, with interstitial

[1] The presence of liver-cell emboli in the lung capillaries and in the heart clots after traumatic rupture of the liver, and in infectious diseases involving local necroses of the liver, has been described by various observers. Emboli believed to be composed largely of placental cells or of cells from the bone-marrow are also described under various conditions. The facts relating to this subject of parenchyma-cell emboli and its alleged significance may be found summarized by *Lubarsch*, Fortschr. d. Med., 1893, xi, 805, 845; and by *Aschoff*, Virchows Arch., 1893, cxxxiv, 11. Consult also *Warthin*, Med. News, 1900, lxvii, 405 (bibl.).

hemorrhage by diapedesis and more or less necrosis of the involved area, are called *hemorrhagic infarcts* (Fig. 13).

After a time the infarct becomes decolorized by diffusion of the dissolved hemoglobin, inflammatory changes occur in its periphery, the blood-cells and involved tissues may undergo degeneration and be absorbed,[1] and finally the seat of the infarction may be indicated only by a mass of cicatricial tissue, which frequently contains more or less pigment.

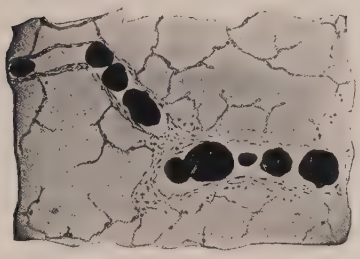

FIG. 11.—FAT EMBOLI IN THE BLOOD-VESSELS OF THE LUNG.
This followed bone fracture.

In another class of cases, instead of an excessive distention of the vessels and an extravasation of blood in the affected region the tissue is simply deprived of nourishment and undergoes necrosis. The affected area then sooner or later becomes lighter in color from the diffusion of the hemoglobin, and is called an *anemic* or *white infarct* (Fig. 14).

Inflammatory changes may occur in its periphery and a new connective tissue capsule form around it, and the dead mass may thus persist for some time, or be gradually absorbed and replaced by cicatricial tissue. In certain instances it is believed that infarcts may be anemic from the beginning and not, as is apparently usually the case, as the result of changes in infarcts which are at first of the hemorrhagic type.

The scope of this book does not permit us to consider the somewhat complicated and often obscure reasons why in one case there is hemorrhagic, in another white, infarction, as a result of embolus.

If the embolic material consists of or contains infective substances, such as some forms of bacteria, in addition to the mechanical effects of simple emboli, we may have gangrene, suppuration, formation of abscesses, etc., as the result of the local action of the infectious material, even though this may be present in very small amount.

FIG. 12.—INFARCTS OF THE SPLEEN.

The Location of Infarcts.—The organs in which embolic infarctions most frequently occur are the spleen, kidney, brain, lungs; less frequently the heart, retina, liver, and small intestines.

Hemorrhagic infarction is not liable to occur in the *liver* from emboli in the branches of the portal vein, on account of the blood supply which may come to the affected region through the branches of the hepatic artery. On the other hand, embolic abscesses from infectious emboli are of not infrequent occurrence here.

[1] For a study of the autolytic processes in the absorption of infarcts, see *Wells*, Jour. Med. Research. 1906, N. S. x, 149.

The *lung* is supplied with blood through the pulmonary and the bronchial arteries; and the capillary network of the pulmonary tissue is so abundant that emboli in the pulmonary artery, although this is a terminal artery, do not readily lead to infarction in an otherwise healthy lung. When, however, the pulmonary circulation is disturbed, as in certain forms of heart disease, hemorrhagic infarction may follow embolism of the pulmonary artery.

The arteries of the *kidney* and *spleen* are typical terminal arteries, and infarcts of these organs readily follow embolism. In the kidney the infarcts are most commonly anemic; in the spleen both hemorrhagic and anemic infarcts are formed. Infarction in the *heart* may follow embolism, but is more commonly the result of thrombosis of branches of the coronary artery. Embolism of the *cerebral arteries* is

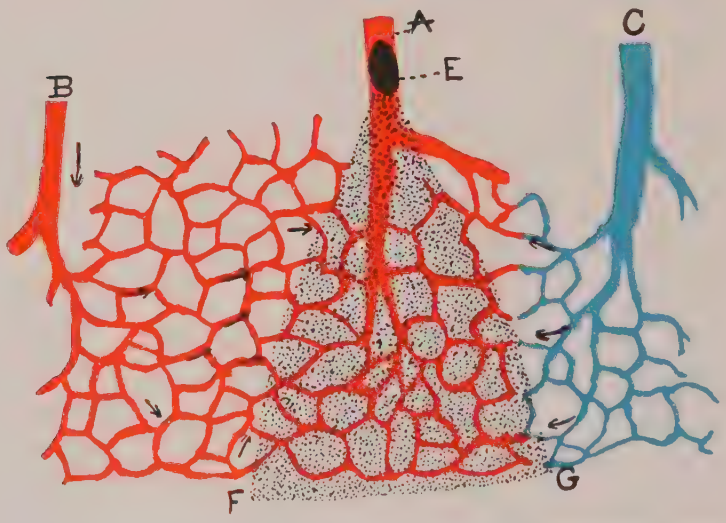

FIG. 13.—DIAGRAM ILLUSTRATING THE FORMATION OF A HEMORRHAGIC INFARCT.

The artery, *A*, plugged by an embolus, *E*, is a terminal artery, though it has abundant capillary anastomoses with the artery *B*, so that the territory deprived of blood is not sufficiently nourished and its tissues die; but from the abundant capillary anastomoses from the artery *B*, and from the vein *C*, a certain amount of blood enters the infarct area, which thus becomes hemorrhagic.

seldom followed by extensive local collateral hyperemia and hemorrhage, but is more apt to lead to cerebral softening. Hemorrhagic infarctions may occur exceptionally in regions not furnished with terminal arteries, as in the *small intestines*. Infarction does not follow embolism of single arterial trunks of the arms and legs because of the ready establishment of a collateral circulation.

Pulmonary Embolism.—From the clinical aspect the most important form of pulmonary embolism is that type which does not give rise to infarction, but causes sudden death. This is seen after childbirth, after surgical operations, especially those on the lower portion of the abdomen, and in conditions in which the circulation of the lower extremities is inter-

fered with, such as crushing wounds, when the muscles are lacerated and the vessels torn, prolonged rest in bed of persons with enfeebled circulation, etc. The thrombi, in these cases, form in the vessels of the calf and also in the femoral veins, as, for instance, where the limb comes in contact with the bed; and the circulation thus being slowed, deposition of blood-platelets occurs with the formation of the type of thrombus described by Aschoff.[1] This thrombus gradually grows centrally into the blood-vessels and, finally, under some mechanical influence is set free in the circulation and passes to the right side of the heart, and then into one of the larger branches of the pulmonary artery, producing in many instances almost instantaneous death. Occasionally, however,

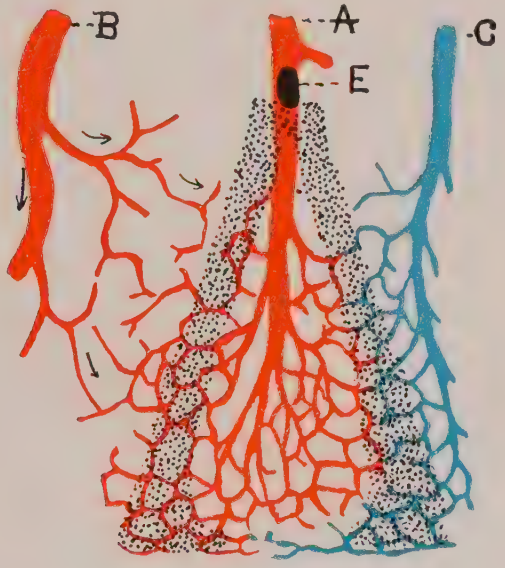

FIG. 14.—DIAGRAM ILLUSTRATING THE FORMATION OF AN ANEMIC INFARCT.

The artery *A* is a terminal artery with a few capillary anastomoses with the neighboring artery *B*, so that when the embolus, *E*, cuts off the blood from the territory supplied by it, the involved region becomes anemic save in the peripheral zone of congestion. This is an anemic infarct.

when the embolus is small, the patient may survive some hours in a condition of shock, deep cyanosis, and labored heart action before death comes. If the amount of lung occluded is still smaller, infarction may result and the patient survive. The condition is unusually serious because it often occurs after relatively simple operations, and happens at the time the patient first gets out of bed, the movement being sufficient to dislodge the embolus. In making post-mortem examinations in the case of such suspicious deaths, it is important that both branches of the pulmonary artery be carefully opened while the heart and lungs are still undisturbed. If this is done, the embolus will frequently be found lying loose in a branch of the artery or even astride one of the bifurcations.

[1] *Aschoff, L.*, Zieglers Beitr., 1912, lii, 205.

It is usually soft and red, and occasionally shows the marks of the valves of the veins with which it has been in contact. The frequency of such emboli varies considerably. While thrombosis occurs in about 1 per cent. of laparotomies for pelvic trouble, fatal embolism has been noted in different series of cases in from 0.1 to 0.2 per cent., though individual series may show considerably higher figures; for example, Zurhelle[1] reports that after myoma operations there were emboli in the lungs in 1.5 per cent. of the cases. That infection has nothing to do with this type of thrombosis is shown by the fact that the introduction of aseptic technique has not diminished the number of fatal emboli.[2]

The Sources of Emboli.—It should be remembered that as a rule emboli derived from a vein, and then most commonly detached from a venous thrombus, pass to the right side of the heart and are thence driven into the pulmonary artery, where, unless most minute, they are retained, since they cannot pass the pulmonary capillaries. Emboli in the left heart, the aorta, and the arterial system are derived from the pulmonary vein, the left heart, the aorta, or its branches (Fig. 15).

Paradoxical Embolism.—While as a rule emboli follow the direction of the blood-current, one does sometimes find in the arterial system emboli of considerable size without being able to locate their source in the pulmonary vein, the left heart, or the aorta or its larger branches. Furthermore, under these circumstances one may discover an obvious source in the systemic veins. Since such emboli cannot pass the pulmonary capillaries they must have passed from the venous to the arterial system through an open foramen ovale into the left auricle, thence to be driven into the arteries (Fig. 15). This is called *paradoxical embolism.* It is of infrequent occurrence.[3]

Retrograde Embolism.—Sometimes an embolus moves in a direction opposite to that of the blood-current, so that one may find in a small vein an embolus obviously derived from a larger vein or from the right heart. It has been assumed in explanation of this occurrence that under certain conditions in which the venous blood empties itself into the right heart with difficulty, as in the case of tricuspid incompetence, there might be an actual reversal of the venous current on which an embolus could be conveyed. It does not, however, appear that such a reflux of the venous blood is possible. Ribbert urges the view that while a complete reversal of the current is improbable in a congested vein, a pulsation wave may form with each heart-beat which could gradually force the embolus toward the periphery along the vessel wall. This retrograde transportation of an embolus is of rare occurrence in the large veins, especially in the inferior vena cava.

The retrograde transportation of particles of tumor may give rise to very puzzling phases of metastasis.

[1] *Zurhelle, E.*, Arch. f. Gynäk., 1908, lxxxiv, 443; Zieglers Beitr., 1910, xlvii, 539 (bibl.).

[2] For a full discussion of the question, see *Aschoff, L.*, Beiträge zur Thrombosefrage, Leipzig, 1912; reprinted from Verhandl. d. Natursforsch. Gesellsch, 1911, p. 344; *Ranzi*, Arch. f. klin. Chir., 1918, lxxxvii, 380; *Cutler, E. C.*, and *Morton, J. J.*, Surg., Gynec., and Obst., 1917, xxv, 621; *Fränkel*, Arch. f. klin. Chir., 1908, lxxxvi, 531; and *Wilson, L. B.*, Ann. Surg., 1912, lvi, 809.

[3] For details of unusual forms of embolism consult bibliography in *Ziegler's* General Pathology, English trans., 11th edition, New York, 1921.

Fat Embolism.—After fracture of the long bones, fat from the marrow may find its way through opened veins into the right heart and into the pulmonary capillaries (Fig. 11). It may be found also in the capillaries of the kidneys. Fat embolism of the pulmonary capillaries

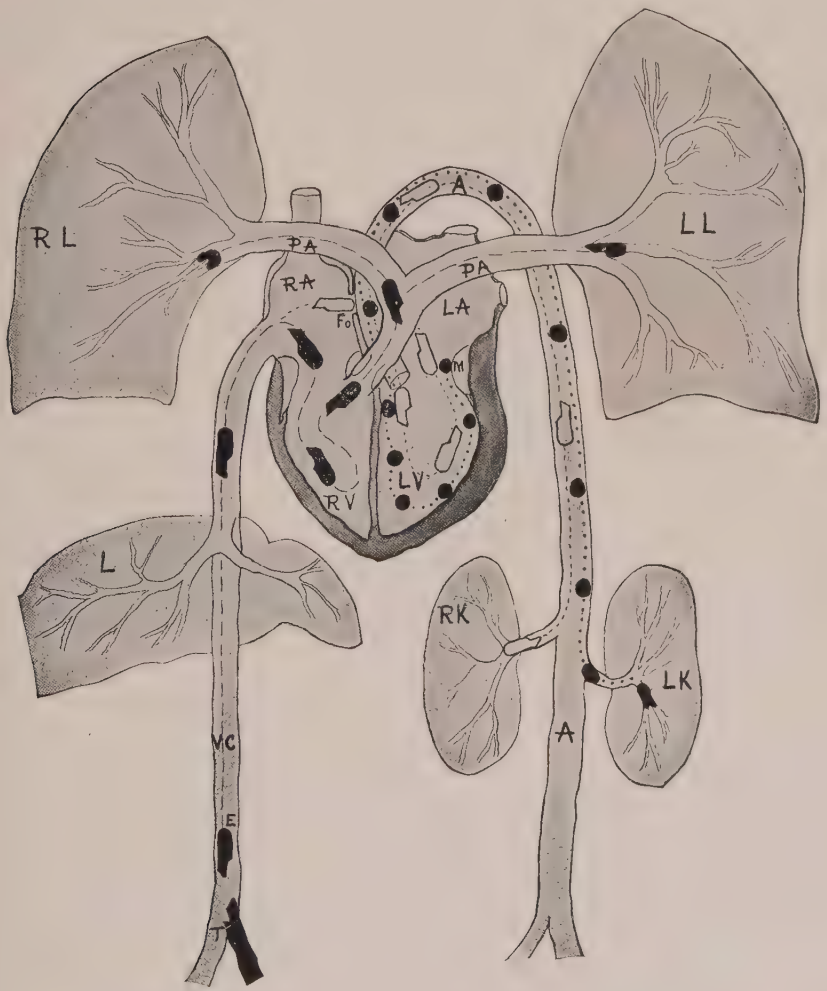

FIG. 15.—SCHEMATIC ILLUSTRATION OF EMBOLISM—AFTER RIBBERT.

The right lung, *RL*, and the left lung, *LL*, are connected with the heart through the pulmonary artery, *PA*, *PA*. The liver, *L*, and the right and left kidneys, *RK*, *LK*, are seen below with the aorta *A* and the vena cava, *VC*. The right ventricle, *RV*, and the left ventricle, *LV*, the right auricle, *RA* and the left auricle, *LA*, are exposed. From the thrombus *T*, a small portion, *E*, is detached and carried upward in the venous current through the vena cava to the heart. It turns into the pulmonary artery where it may lodge in the larger trunks in the lungs. Owing to its size it cannot pass the capillary system of the lungs, and hence cannot enter the general circulation. If, however, as is not infrequently the case, an open foramen ovale exists, such an embolus could pass through the septum into the left heart, whence it could be sent through the aorta to the viscera, as is shown by the outlined embolus. A thrombus in the left heart, say on the mitral valve at M, if detached as is shown in the globular mass following the dotted line, may be sent into the aorta and thence into any of the small arterial trunks. In the diagram the embolus is lodged in the left kidney.

may be fatal, but in most cases does not appear to be of great significance. Fat embolism of the lungs is recorded following extensive fatty degeneration of the liver in phosphorus poisoning and severe kidney lesions.[1] It is thought that there may be some correlation between shock due to severe injuries and fat embolism.[2]

Emboli of Tumor Cells.—Clusters of tumor cells of considerable size may enter the vessels through erosion of their walls and may be transported in the blood-current as emboli (Fig. 202, p. 388). They may lodge in the trunks of large vessels, portal vein, pulmonary artery, etc., and in addition to the usual effects of embolism they may grow, forming metastatic tumors. Undoubtedly, only a small proportion of the tumor emboli which reach the organs ever develop into tumors. The majority are destroyed by encapsulation with fibrin and by the action of the ferments of the blood.[3]

Air Embolism.—It rarely happens in surgical operations that a large quantity of air enters an opened vein and is aspirated to the right side of the heart. This may prove fatal. Air bubbles may be found mingled with the blood in the right heart, in the large veins leading to the heart, and in the pulmonary capillaries. Small quantities of air may enter the veins without having the slightest effect on the patient's condition; and the presence of a few air bubbles in the blood at autopsy is not an evidence that air had entered through a wounded vessel or that the patient's death was caused thereby. Researches on animals have showed that large quantities of air can be injected directly into the circulation without causing serious symptoms.[4] The presence of gas in the vessels is common in caisson disease (page 22). In certain cases gas bubbles in the blood are due to infection with a gas-forming bacterium, the Bacillus aërogenes capsulatus (page 327).

Experimental Study of Disturbances of the Circulation.

One may observe many of the local disturbances of the circulation on the mesentery of the curarized[5] frog. A loop of the intestine is drawn out through a lateral abdominal incision and laid over the glass window of a Thoma frog-plate (see Fig. 77). The part should be kept moist or irrigated with 0.6 per cent. salt solution. Under these conditions one may study various phases of hyperemia and stasis, hemorrhage by diapedesis and by slight injuries to the vessels, hemorrhage by rhexis and the formation of local thrombi by which it is controlled. By pressure on the vessels various disturbances of the circulation, thrombi, etc., can be secured.[6]

[1] For a study of fat embolism see *Connell*, Jour. Am. Med. Assn., 1905, xliv, 612; and *Katase, A.* Cor.-Bl. f. schweiz. Aerzte, 1917, xlvii, 545; for a study of fat emboli of the brain, see *Naville* and *Fromberg*, Arch. de méd. expér., 1913, xxv, 405; and *Gröndahl, N. B.*, Deutsch. Ztschr. f. Chir., 1911, cxi, 56.

[2] *Porter, W. T.*, New York Med. Jour., 1917, cvi, 894.

[3] *Schmidt, M. B.*, Die Verbreitungswege des Karcinome, Jena, 1903.

[4] See *Goodridge, M.*, Am. Jour. Med. Sc., 1902, cxxiv, 461 (bibl.); *Hare, H. A.*, ibid., p. 843; and *v. Oppel*, Deutsch. Ztschr. f. Chir., 1908, xcii, 437.

[5] The commercial curare is so variable in strength that it is best to make an aqueous solution of about 1:1,000 strength and test the effect, using just enough to secure immobility, and no more, since serious circulatory disturbances and death of the animal are readily induced with too liberal dosage. The solution—at first a few drops—is put beneath the skin in the dorsal lymph sac. It is well to give a preliminary dose a few hours before the use of the animal, bringing him partially under the influence of the drug, and to complete the effect just before the experiment. Under these conditions the second dose may be very small and thus untoward effects upon the circulation may be avoided.

[6] See for a further description of the method of studying the circulation in the living frog, p. 131.

By drawing forward the tongue of the curarized frog, fastening it in extension on the Thoma frog-plate designed for this purpose (Fig. 77), and ligating one of the large lateral veins, one can induce interesting phases of passive hyperemia and transudation.

Embolism may be studied by the injection into the arteries of small particles—tobacco seed in the dog, begonia seed in the rabbit, or poppy seed—suspended in salt solution. These may be injected forcibly upward through the crural artery into the aorta. Embolism of the abdominal viscera, kidney, spleen, etc., with infarction may be thus induced.

CHAPTER III.

REGRESSIVE TISSUE CHANGES.

General Considerations.

THERE are three phases of activity in the transformations of energy which are characteristic of living cells. These are nutrition, reproduction, and functional activity. But while these manifestations of energy are more or less distinct as properties of living matter, they are closely interdependent. It is the suitable balance of these activities fixed by prolonged environment which determines what we call health. When this balance is disturbed beyond the limits of physiological variation, the alterations which result may be manifest, either in the diminution or destruction of tissue or in its increase or new formation. In other words, the cells of the body, when placed under conditions which seriously interfere with the orderly transformations of energy, may undergo alterations from the normal which are *regressive* on the one hand, or *progressive* on the other.

We shall in this chapter consider the regressive processes and their effects; in the next those which are progressive.

It is well to remember that the regressive as well as the progressive changes in the body are not limited to pathological conditions, but form a part of the normal processes through which growth is secured and function maintained.[1]

The maintenance of the normal life and structure of the cell is closely dependent upon the conditions under which it is placed. If there is lack of sufficient or proper nutriment; if the waste products are not properly eliminated; if deleterious chemical substances either coming from without or formed by defective metabolism—poisons, toxins, etc. —are present; or if harmful physical agencies such as heat, cold, pressure, etc., are active; or, finally, if the innervation be defective, both the function and the structure of the cell may suffer.

The functional changes of cells placed under unfavorable conditions are very variable and often very subtle owing to their complex and but little understood nature, and may be difficult of detection. These functional changes may or may not be associated with structural alterations which are obvious on microscopical observation. Cells may become larger than normal through increased functional activity, *hypertrophy;* they may become smaller, *atrophy*, under a variety of conditions presently to be considered. Cells may swell through imbibition of fluid; they may be altered in shape from pressure. Finally, they may suffer various

[1] For a résumé of the relationship between normal and pathological regressive processes see *Minot*, Middleton Goldsmith Lecture on The Embryological Basis of Pathology, Science, 1901, xiii, 377, 481.

changes in internal structure. Various products of their metabolism or of degeneration of their cytoplasm may accumulate within them, or substances may enter from without—*degeneration* and *infiltration.*

These and other changes due to an unfavorable environment may be recovered from, if not too extensive. But, on the other hand, if the damage be excessive the cell may die and suffer disintegration and absorption. This death of the cell, with subsequent physical and chemical changes, is called *necrosis.*

It frequently happens, however, that the vitality of the cell is not at once extinguished, but that the processes of life and necrosis go on for a time together, ending in either its recovery or its death. This condition is called *necrobiosis.*

Not all the cells of the body are equally sensitive to a deleterious environment. It is those which are more highly differentiated for the performance of special functions, or those which are more frequently exposed to harmful influences, which most often suffer.

Atrophy.

Atrophy is a diminution in the size of the body, of organs, or of tissue elements. It occurs as a physiological process in man as well as in certain of the lower animals. Thus in man the thymus and the umbilical vessels undergo atrophy at an early period; while in old age, atrophy of the sexual organs and of the tissues in general is the usual mark of senil-

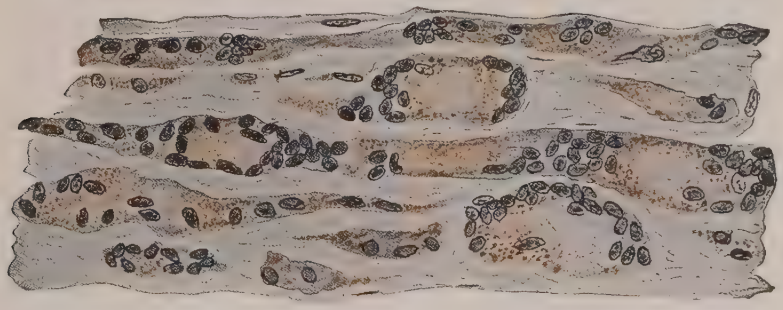

FIG. 16.—ATROPHY OF MUSCLE.
This is atrophy from disuse of the striated muscle. Owing to the muscle pigment which has collected in the atrophied fibers this is called "pigment atrophy."

ity.[1] On the other hand, as a pathological process, atrophy may occur in connection with disturbances of innervation or nutrition; from disuse or from pressure; or from the presence of poisons. Although it is convenient to name these as phases of atrophy, they are not fundamentally distinct. In *simple atrophy*, under whatever conditions it may occur, the tissue elements become smaller without marked alterations in structure,

[1] For a study of the changes in the body in development and senility see the monographs of *Mühlmann, M.*, Über die Ursache des Alters, Wiesbaden, 1900; Das Altern und der physiologische Tod, Jena, 1910 (bibl.); and Virchows Arch., 1914, ccxv, 1; *Minot, C. S.*, The Problem of Age, Growth, and Death, New York, 1908; *Child, C. M.*, Senescence and Rejuvenescence, Chicago, 1915.

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and may finally disappear altogether. In the majority of cases, however, atrophy of cells or other tissue elements is not simple, but is associated with, and often determined by, various phases of degeneration—*degenerative atrophy*. The cytoplasm of atrophic cells is often more transparent than normal and may contain an undue proportion of pigment.

An organ which is the seat of even extensive atrophy of some of its

Fig. 17.—Atrophy and Distortion of the Liver from Tight Lacing—Female. The border of the organ is elongated and fibrous; the gall-bladder is long and distorted.

cells is not necessarily diminished in size, but may even be much larger than normal. This is the case, for example, in amyloid degenerations of the liver. Sometimes the atrophy of parenchyma cells is accompanied by a new formation of connective tissue so extensive as to maintain, for a time at least, the size of the organ.

Atrophy may be general or local and it has various phases which we shall briefly consider.

General Atrophy from Malnutrition affecting the body at large may occur as the result of deficient nutriment as in starvation, or a failure to assimilate food, and in various acute and chronic diseases. Under these conditions fatty and other forms of cell degeneration occur, with loss of the general adipose and reduction in size of muscle and other body cells.

Senile Atrophy.—As the energies of life decline with the advance of years, the tissues and organs may undergo gradual and progressive atrophy, but in varying degrees. The muscle cells of the heart are more slender, and brown pigment may accumulate within them—*brown atrophy*. The parenchyma cells of the liver, kidney, and generative

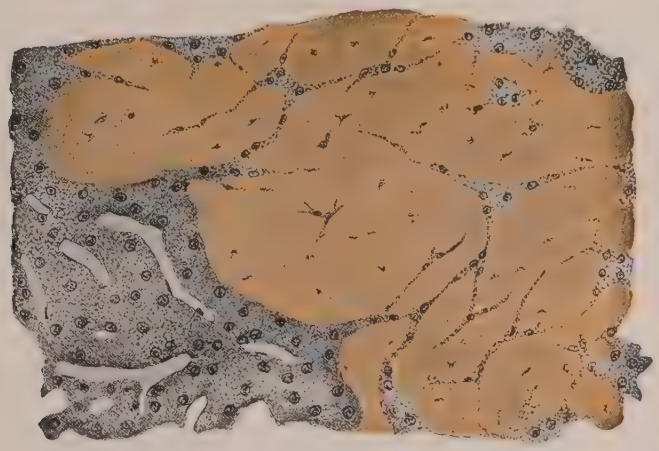


FIG. 18.—ATROPHY OF LIVER CELLS.
Pressure atrophy from amyloid degeneration of the blood-vessels.

glands and the ganglion cells become smaller and may be more or less pigmented. Similarly the bones suffer atrophic changes, becoming more brittle, and the skin becomes wrinkled and dry. Senile atrophy may be associated with significant sclerotic changes in the blood-vessels and with atrophy of the lymph-nodes, spleen, and marrow.

Atrophy from Suspension of Functional Activity—Atrophy from Disuse.—This is well exemplified in disused muscles or bones, as in various forms of paralysis. Voluntary muscles under these circumstances become more slender, lose their transverse striations, and become fibrillar. Brown pigment derived from the disappearing muscle substance may gather in masses in the remaining fibers, and the nuclei of the sarcolemma may be increased in number (Fig. 16). The fibers may finally disappear and may be replaced by fat or fibrillar connective tissue.

Pressure Atrophy.—This is seen under the ordinary conditions of modern life as the result of ill-adapted articles of dress, such as corsets, which frequently induce very marked atrophy with distortion of the liver (Fig. 17). But within the body itself pressure from a more vigorously growing tissue may induce atrophy of an adjacent part. Thus,

tumors, cysts, accumulations of fluids in various cavities, aneurysms, degeneration of blood-vessels (Fig. 18), etc., may lead to local atrophy.

Neurotic Atrophy.—While it is difficult to dissociate the direct trophic influence of the nerves upon tissues from the accompanying loss of function and interference with vascular supply, there appear to be cases of atrophy from neurotrophic influences. Atrophy of one side of the face in lesions of the trigeminus and in certain cerebral lesions, wasting of the associated muscles in destruction of the anterior cornua of the spinal cord, are examples.

Degeneration.

ALBUMINOUS DEGENERATION (Cloudy Swelling, Parenchymatous Degeneration, Acute Degeneration, Granular Degeneration).

Under a variety of conditions in which there is a disturbance of cell metabolism, but especially often in infectious diseases and in intoxications when poisonous substances come in contact with the tissues, the cells of the body show an accumulation in the cytoplasm of albuminous granules of various sizes and forms. While bacterial toxins are common excitants of this change, other vegetable toxins, such as abrin and ricin, or mineral poisons, as corrosive sublimate, may induce it. This is a type

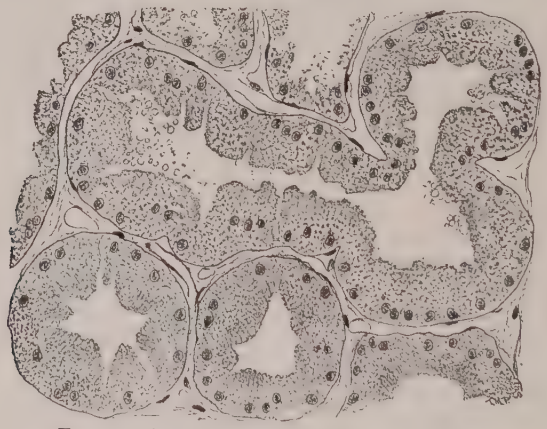


FIG. 19.—ALBUMINOUS DEGENERATION—KIDNEY.
The lesion is moderate in degree and is most marked in the largest tubule above.

of cell degeneration which is so often associated with infectious diseases and certain phases of inflammation that it is sometimes regarded as a part of the inflammatory process. The cells in this condition are usually swollen and are more opaque than normal, the nucleus being usually somewhat concealed in the granules when these are numerous (Fig. 19). The albuminous granules in the cells are soluble in dilute acetic acid, but not in ether, being thus distinguished from fat.

While all the cells of the body are subject to this phase of protoplasmic degeneration, it is most pronounced and frequent in the paren-

chyma cells of the liver and kidney, in muscle, and in epithelial cel of the mucous membranes. These are, it will be seen, cells which have a large amount of cytoplasm and in which metabolism is active and the exigencies of nutrition are imperative. The alterations in the ganglion cells of the central nervous system in infectious diseases and in various forms of intoxication are somewhat different from those occurring in other parenchyma cells and will be described in the section devoted to the Brain and Spinal Cord.

Cells in a condition of albuminous degeneration may return to their normal state, they may become fatty, or they may die, become necrotic, and disintegrate.

The liver, kidney, muscle, mucous membranes, etc., when in this condition, are often swollen and in gross appearance more opaque and gray than when normal.

The exact chemical nature of this degenerative process is obscure and will doubtless remain so until we know much more than we now do of cell structure and cell metabolism.[1]

Technique.—The microscopical study of this lesion is best made in fresh frozen sections of the tissue, either after formalin fixation, or in fresh tissue teased in 0.85 per cent. salt solution.

FATTY DEGENERATION AND FATTY INFILTRATION.

General Considerations.

It should be remembered that besides the occurrence of fat cells in fat tissue and in the interstitial tissue of various organs, the accumulation of fat in certain epithelial cells is physiological, as in the functional processes of the mammary and sebaceous glands.[2] In the involution of the uterus—also a physiological process—extensive fatty metamorphosis of cell protoplasm occurs.

It is customary and convenient, in considering the abnormal accumulation of fat in the tissues, to assume that in one set of cases—fatty degeneration—the fat is formed by a retrograde metamorphosis or degeneration of the protein elements of protoplasm, a process by which the integrity and capacity of the cell are compromised, while in the other—fatty infiltration—it may be due to a simple accumulation in the cell of fat formed elsewhere—a condition of less significance.

The validity of this assumption has of late been called in question. It involves in large measure the solution of the physiological problem whether normally the fat in the body is formed from proteins or from carbohydrates. Concerning this, many experiments and much argument have been made;[3] but it appears not yet to be solved. The traditional

[1] For a study of albuminous degeneration see *Albrecht*, Verhandl. d. deutsch. path. Gesellsch., 1903, vi, 63.

[2] For chemistry of fats, see *Mathews*, Physiological Chemistry, 2d edition, New York, 1917, chap. iii; and *Fischer* and *Hooker*, Fats and Fatty Degeneration, New York, 1917.

[3] For a critical summary of this question see *Taylor*, Am. Jour. Med. Sc., 1899, cxvii, 569; and *Albrecht*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907, xi[2], 1166. For a study of the rôle of soluble soaps in formation of fat in cells, see *Klotz*, Jour. Exper. Med., 1905, vii, 633; also *Albrecht*, foot-note above. For a study of myelinic substances in cells, see *Albrecht*, Verhandl. d. deutsch. path. Gesellsch., 1903, vi, 95; and *Adami*, Jour. Am. Med. Assn., 1907, xlviii, 463.

distinction between fatty degeneration and fatty infiltration will therefore be made here, with such modifications and reserve as are fitting in view of our lack of knowledge.

There is apparently a certain amount of fat or closely related substances in the cytoplasm of many cells not demonstrable morphologically. Similarly there is fat in the blood which may be conveyed to cells. Under normal conditions these forms of fat enter into the metabolism of the cells and are used up.

We might perhaps wisely adopt the conception of Ribbert that fatty degeneration is a condition in which the involved cells are so damaged through various harmful agencies that the fat which they may normally contain, but which is invisible in their cytoplasm, or fat taken into the cell from without, or fat formed in the cell metabolism, is not properly metamorphosed—burned—but accumulates in droplets in the cell body. The appearance of fat in connective-tissue cells growing in vitro affords support to this idea, as extracellular transport in this case is impossible.

Fatty Degeneration.

In fatty degeneration there is an accumulation of larger and smaller droplets of fat in the cell, sometimes so slight as to be scarcely visible, sometimes so great as largely to replace the protoplasm, crowding the nucleus to one side. These strongly refractile fat droplets are not changed by dilute acetic acid. They are soluble in ether, and when fresh

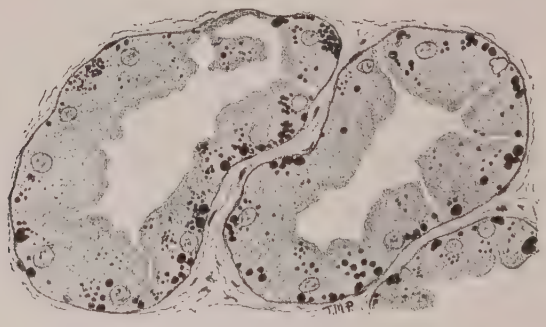


Fig. 20.—Fatty Degeneration—Kidney.
The fat droplets are stained black by osmic acid.

are stained black by osmic acid (Fig. 20), red by Sudan III or Scharlach R. (Fig. 21), and red or blue by Nile blue sulphate (see technique below). Not infrequently, feathery clusters of delicate fat crystals are present in the cells. Cells in excessive fatty degeneration may disintegrate, forming an oily detritus in which, especially when much moisture is present, cholesterin crystals may form by decomposition of the lipoids.

To the naked eye, organs in a condition of marked fatty degeneration are usually larger and softer than normal, have a grayish-yellow color or

are mottled with yellowish streaks or patches, and the normal markings of cut surfaces are more or less obscured.

Fatty degeneration may be associated with or may follow albuminous degeneration and may occur under similar general conditions, as in infections, poisoning, etc. It is often associated with the processes of necrosis and disintegration in dead cells and dead tissue. It may be due to local or general disturbances of nutrition, from a great variety of causes—disturbances which either directly affect the life processes of

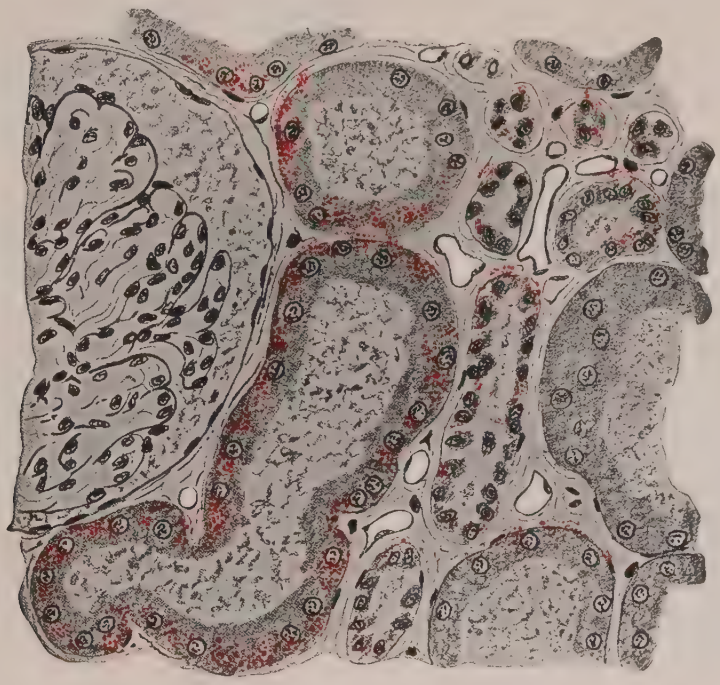


Fig. 21.—Fatty Degeneration of Epithelium in the Kidney
The fat droplets are stained with Scharlach R.

the cells themselves or which produce alterations in their nutritive supply. In addition to its local occurrence, as a result of local disturbances of circulation in the vicinity of inflammations or in tumors, etc., it is apt to occur in the liver, heart muscle, and kidney in chronic exhausting diseases and in conditions and diseases to which profound anemia is incident, in senility, or as the result of the action of certain poisons, such as phosphorus and arsenic.

The function of the cell in fatty degeneration may be greatly impaired, as in fatty degeneration of the heart muscle. On the other hand, in the liver and kidney, the function of the organ may not apparently suffer even with marked degrees of the lesion. The cell may recover if the lesion be not too profound.

Fatty Infiltration.

This is of common occurrence under normal as well as pathological conditions. The fat is believed to originate outside of the cells, accumulating in them, and inducing a passive atrophy of the cytoplasm. Cells in a condition of abnormal fatty infiltration are scarcely to be distinguished morphologically from those involved in fatty degeneration. The presence in the cells of large or small droplets of fat, without marks of degeneration in the remaining protoplasm, has been regarded as distinctive of infiltration.

In some phases of fatty infiltration, as in the heart (Fig. 22) or the pancreas, for example, the fat accumulates in the cells of the interstitial

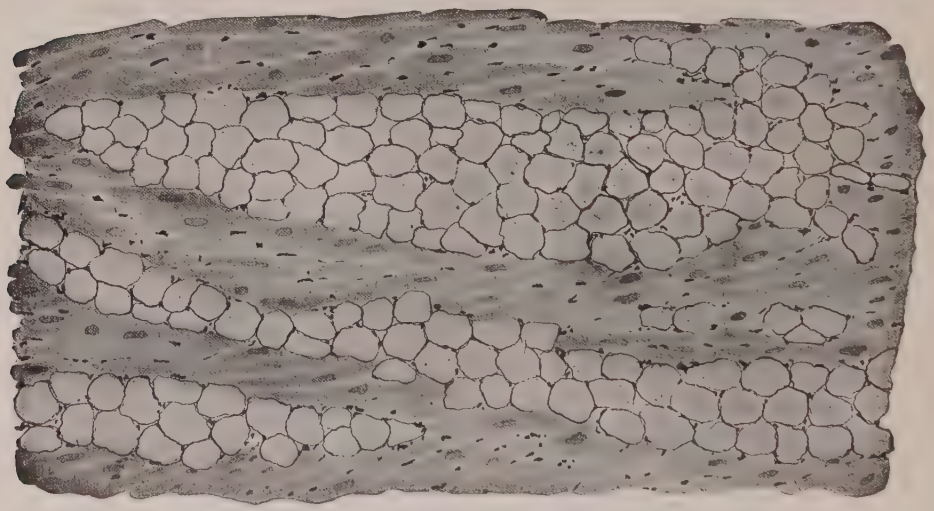


Fig. 22.—Fatty Infiltration of the Heart.
The fat cells have accumulated *between* the muscle cells of the heart, and not *within* them as in fatty degeneration.

connective tissue in a manner identical with that in which the normal panniculus adiposus is formed. The heart muscles or the gland cells are under such conditions, affected secondarily through pressure atrophy from the accumulated fat. It should be remembered that fatty infiltration and fatty degeneration may occur simultaneously. When fat production or fat storage is largely in excess of fat consumption from either local or general causes, the condition is called *lipomatosis* or *liposis*.[1]

Lipoid Degeneration.—In the cortex of the adrenal and in the lutein cells of the ovary double refractive granules occur normally. Similar granules are found in atherosclerotic areas in the vessels, in some of the

[1] For a study of lipomatosis with bibl., see *Lyon*, Arch. Int. Med., 1910, vi, 10; and *Matsuoka*, Jour. Path. and Bacteriol., 1915, xx, 85.

nephritides, in the walls of old abscesses, and in the gall-bladder with biliary stasis, also in the so-called adrenal tumors of the kidney, in adenomata of the adrenal, and in xanthomata of the skin. These granules are composed of a combination of cholesterin and fatty acid in the form of an ester (Fig. 23).[1]

FIG. 23.—LIPOID GLOBULES IN JUICE EXPRESSED FROM SUPRARENAL. Viewed under crossed Nicols.

Technique.—Frozen sections should be made of fresh tissues, which may then be examined in 0.85 per cent. salt solution with crossed Nicols for double refracting fat; or frozen sections of fresh tissue or that hardened in formalin can be stained for twenty minutes in a saturated solution of Sudan III or Scharlach R in equal parts of acetone and 70 per cent. alcohol, washed in 70 per cent. alcohol, transferred to water, and mounted in glycerin or glycerin jelly. A saturated aqueous solution of Nile blue sulphate (Grübler) will also stain fat satisfactorily. With this stain the neutral fat is red, the nuclei blue, and the fatty acids dark blue. The granules which stain a purplish color are lipoids. It is an advantage, according to Schmorl, to wash the section in 1 per cent. acetic acid, and then in water, and embed in glycerin or glycerin jelly.[2]

GLYCOGEN INFILTRATION.

Glycogen appears under abnormal conditions in the cells as hyaline, mostly globular masses of varying size (Fig. 24). It is soluble in water, is stained brownish-red by iodine, and does not, like amyloid, assume a greenish color by further addition of sulphuric acid. In diabetes it may occur in large quantities in the liver cells and in the epithelial cells of the uriniferous tubules, especially in those of Henle's loop, and in leucocytes. It may be found in fresh pus cells, in the cells of various forms of tumors, and in leucocytes in the blood in leukemia, in chronic diseases of the gastrointestinal tract in children, and in various acute and chronic diseases.[3]

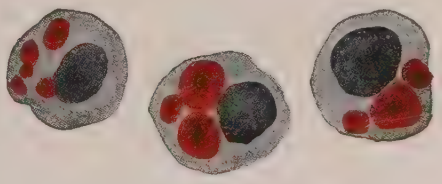


FIG. 24.—GLYCOGEN INFILTRATION OF EPITHELIAL CELLS. The droplets of glycogen are stained with iodine.

TECHNIQUE.—If the tissue to be examined for glycogen be fresh, the iodine should be used in solution in glycerin (equal parts of Lugol's solution and glycerin), in order

[1] Closely related to these esters, but differing from them by a lack of double refraction, are the so-called myelin bodies which appear in tissues undergoing autolysis or decay. They stain with neutral red. For a detailed study of certain of these lipoids see *Bang*, Chemie u. Biochem. der Lipoide, Bergmann, 1911; *Kawamura*, Cholesterinesterverfettung, Jena, 1911; and *MacLean, H.*, Lecithin and Allied Substances: The Lipins, London, 1918.

[2] For method of staining fat-acid crystals see *Mallory* and *Wright's* Pathological Technique, 6th edition, 1915, p. 406. For details of staining fat and lipoid substances see *Schmorl*, Pathologischen Unterchungsmethoden, 7th edition, Leipzig, 1914, p. 159. For recent improvements in the identification of different types of fat, see *Bell, E. T.*, Jour. Path. and Bacteriol., 1914–15, xix, 105.

[3] For general review with bibl., see *Gierke, E.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907 xi², 871.

to avoid its solution. If specimens are to be hardened, this should be done in absolute alcohol to avoid the solution of the glycogen. Sections of material hardened in alcohol are stained for 5 to 10 minutes in Lugol's solution; dehydrated in a mixture of absolute alcohol, 4 parts, and tincture of iodine, 1 part; cleared; and preserved in oil of origanum. The preferred method is that of Best.

SEROUS INFILTRATION OF CELLS (Hydropic Degeneration, Vacuolization).

Under many pathological conditions, cells, especially those of mucous membranes, glands, muscles, tumors, etc., contain one or more larger or smaller droplets of clear fluid (Fig. 25). The cell may thus be distended. These droplets are usually extranuclear and may crowd the nucleus to one side of the cell. The nature and source of this accumulated fluid are not definitely known. Its transparent appearance in the granular protoplasm has given rise to the term "vacuole." It may be associated with general tissue edema, with inflammatory and degenerative processes, etc.

Mucous and Colloid Degeneration.

There is a group of closely related translucent glycoprotein substances which it was formerly thought practicable to distinguish by simple chemical tests, especially relating to solubility. Among these are the so-called mucins and colloid. The simplicity of the earlier distinction has,

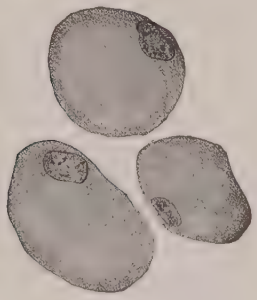


FIG. 25.—SEROUS INFILTRATION OF EPITHELIAL CELLS.

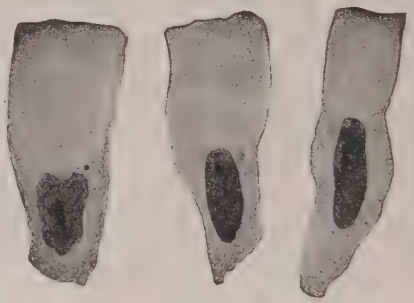


FIG. 26.—MUCOUS DEGENERATION OF EPITHELIAL CELLS.
From a cystadenoma of the ovary.

however, not been justified by more modern research, so that the separation of mucous and colloid degeneration along the old lines does not express very definite chemical knowledge. It will, however, be convenient, while awaiting light from the chemist, to maintain the old distinctions between mucous and colloid degeneration, unstable as are the foundations on which they rest.

MUCOUS DEGENERATION.

Mucous degeneration may occur in cells or in intercellular substance. When occurring in cells it consists, under pathological as under normal conditions, of the transformation of the protoplasm into a translucent, ropy, semifluid material, occupying more space than the unaltered protoplasm and hence causing a swelling of the cells (Fig. 26). The distention of cylindrical epithelium by the accumulation of mucin-containing

substances in the outer portion of the cell, with the crowding of the nucleus and the remnant of the cytoplasm toward the base, often gives the cells the shape of a goblet or beaker (Fig. 27), hence the name "beaker cells," often applied to them. This appearance is especially well marked when the mucinogenous contents of the cell have been discharged from the free end.

Mucins may collect in small transparent droplets within cells or may

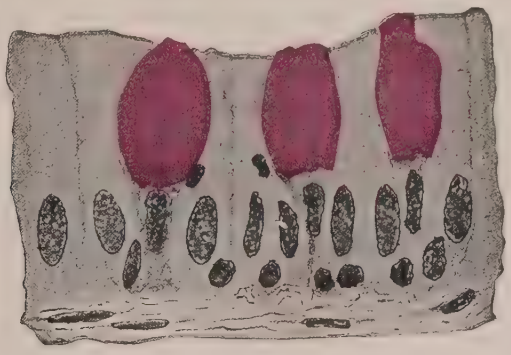


FIG. 27.—"BEAKER CELLS."
Formation of mucus in the epithelium of the small intestine. The mucus is stained with thionin.

so distend them as to form a globular body with a scarcely visible remnant of nucleus or cytoplasm. The cells may be totally destroyed by the accumulation of the mucinous material within them. This newformed material contains mucin in solution, which is precipitated by acetic acid and by alcohol. It swells up in water and is readily stained

FIG. 28.—MUCOUS DEGENERATION OF FIBROUS TISSUE OF MAMMA.

by thionin. It occurs under a variety of conditions, sometimes as an abnormal increase of a normal function of cells, as in many catarrhs, sometimes as an entirely abnormal transformation.

In certain cases, as in many tumors, in cartilage, bone, and other tissues, the intercellular substance may undergo conversion into mucin-

containing material, losing almost entirely its original structure (Fig. 28). The cells in such cases may be affected only secondarily by the pressure which the new-formed material exerts upon them.

TECHNIQUE.—Tissues should be hardened in corrosive sublimate or formaldehyde followed by alcohol; the sections are stained with thionin, mucicarmine, or hematoxylin, which color the mucin-containing portions.

COLLOID DEGENERATION.

This is very closely allied, both in chemical and morphological characters, to mucous degeneration, and in many cases there is no definite microscopic distinction between them. But colloid material, which is normally present in the thyroid, is firmer and more consistent than mucinous, and does not yield a precipitate on addition of acetic acid or alcohol, and its formation is usually confined to cells, not involving intercellular substance, except by an atrophy which its accumulation sometimes induces. The cells may contain larger and smaller droplets of colloid material, or the latter may nearly or entirely replace the protoplasm and accumulate to such an extent as to cause rupture and destruction of the cell. In this way, and by the atrophy of intercellular substance which its accumulation causes, cysts may be formed containing colloid material and cell detritus. Colloid material accumulates frequently in the thyroid gland. A material resembling, if not identical with, colloid is occasionally seen in the form of homogeneous globules in the tubules of kidneys which are the seat of other lesions, in the hypophysis, and in various tumors.

TECHNIQUE.—Tissues should be hardened in formaldehyde or Orth's fluid, and stained with picro-acid fuchsin.

Hyaline Substances.

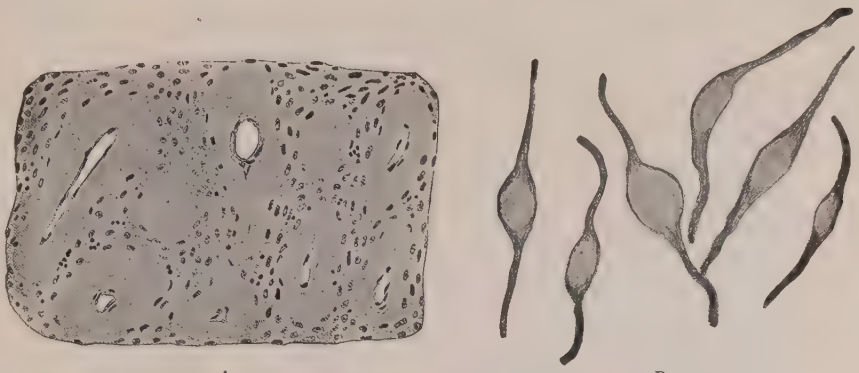
Under a variety of conditions there are deposited in the tissues homogeneous protein substances whose origin and nature are still obscure. Sometimes they are very abundant and seriously interfere with the function of the organs in which they occur. But frequently they are present in small amount and, with or without association with other processes, seem to be of slight importance. While some of these are characteristic in appearance and in the conditions under which they occur, and give definite gross and microchemical reactions, others seem at present to have no definite reactions and appearances, except the homogeneous character which they all share.

One of these substances, *amyloid*, can be definitely differentiated by its appearance, color reactions, and the conditions under which it occurs. Another, *hyaline substance*, while less individualized than amyloid, is conveniently considered for the present as a definite material. The remainder of the homogeneous substances cannot be classified now and are probably of diverse origin and composition.

HYALINE DEGENERATION.

This is the transformation of tissues into a transparent, glassy substance, much resembling amyloid in its morphological characters (Fig. 29), but which does not give the microchemical reactions of amyloid, and appears under different conditions.

Hyaline substance is resistant to the action of acids, and stains readily with acid fuchsin and eosin. It occurs especially in the walls of the smaller blood-vessels in various parts of the body, in voluntary muscle fibers, and sometimes involves interstitial tissue. It occurs in the thyroid, the brain, the reticular tissue of lymph-nodes, and in the



A *B*

FIG. 29.—HYALINE DEGENERATION.

A. In the walls of small blood-vessels from a sarcoma.
B. In muscle cells in infection of pregnant uterus.

ovaries; in the membrana propria of the tubules of the kidney and in Bowman's capsule; in the walls of aneurysms, in the lesions of diphtheria, tuberculosis, and syphilis; in the hyaloid membrane and vessels of the eye, and elsewhere. It occurs in the unstriated muscle fibers in infection of the uterus during pregnancy (Fig. 29). It is believed that fibrin, blood-plates, and leucocytes may undergo hyaline degeneration, and in the form of hyaline thrombi the altered material may block the capillaries in many infectious diseases—typhoid fever, pneumonia, diphtheria, pyemia, etc.—and under other conditions (page 38).

Hyaline substance is not uncommon in coarse trabeculæ or in masses as an apparent modification of fibrin in inflammatory exudates and in thrombi. Hyaline casts are common in the kidney tubules.[1]

TECHNIQUE.—Hardening in alcohol, Orth's fluid, or formaldehyde. Staining by picro-acid fuchsin or by hematoxylin and eosin.

AMYLOID DEGENERATION (Waxy or Lardaceous Degeneration).

This is a process by which the basement substance of various forms of connective tissue, and especially the walls of the blood-vessels, become

[1] Consult for bibliography of studies on hyaline degeneration, *Lubarsch*, Lubarsch-Ostertag Ergebn. d. allg. Path., 1895, i[2], 200; *Davidsohn*, ibid., 1908, xii, 424.

swollen and thickened by their conversion into a translucent, firm, glassy, colorless material, albuminous in character. (For the microchemical reactions of amyloid substance see below under *Technique.*) This albuminous material may be present in the tissues in such small amount as to be recognizable only under the microscope, or it may be so abundant as to give a very characteristic appearance to the tissue. Parts in which the lesion is marked are usually enlarged, and some organs, the liver, for example, may reach a very large size. Affected parts contain less blood and feel harder than normal, and have a peculiar

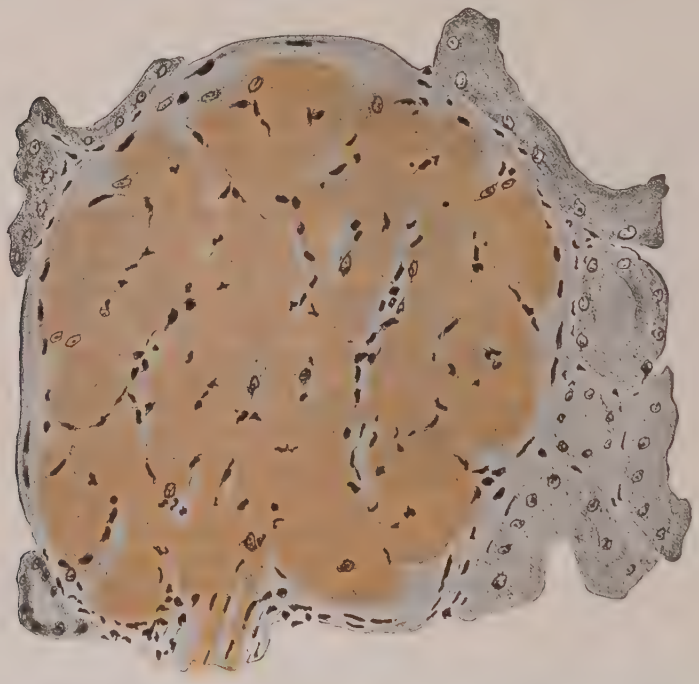


Fig. 30.—Amyloid Degeneration of Capillary Blood-vessels of a Glomerulus of the Kidney. The waxy vessels are stained pink with methyl violet.

shining and translucent appearance which varies in character, depending upon the extent and distribution of the degenerated areas and upon association with other lesions, such as fatty degeneration. It most frequently occurs in the smaller arteries and capillaries (Fig. 30), whose lumen is encroached upon by the thickening of the walls which the process involves. It is usually the media and intermediary layers of the intima which are earliest and most extensively affected. The change also often occurs in the interstitial connective tissue and membranæ propriæ of organs and in reticular connective tissue. It does not affect the parenchyma cells of organs. These, however, frequently undergo atrophy as the result of pressure from the swollen, degenerated tissue.

It is not yet known whether amyloid degeneration is due to a direct

transformation of the tissue, or is an infiltration by some abnormal material formed elsewhere and brought to it, or is derived from the blood.

Amyloid degeneration occurs most frequently and abundantly in the liver, spleen, kidneys, intestinal canal, and lymph-nodes; but it may occur, usually in a less marked degree, in other parts of the body: in the larger blood-vessels, in the interstitial tissue of the heart and mucous membranes of the air passages, and in the generative organs. It may occur locally or appear in various parts of the body at once. It most frequently occurs in connection with severe wasting diseases, particularly in those involving chronic suppuration and ulceration, especially of the bones. It is common in tuberculosis, syphilis, and the cachectic condition induced by malignant tumors, and is occasionally seen in severe malarial infection, dysentery, and leukemia.[1]

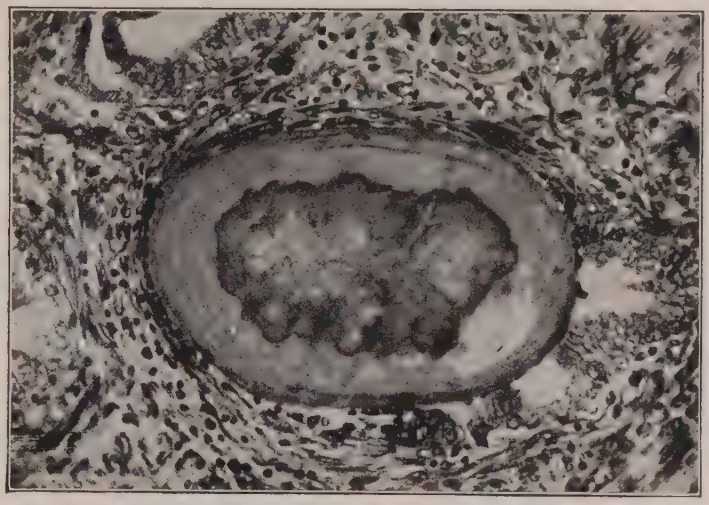


FIG. 31.—CORPUS AMYLACEUM IN A CASE OF CARCINOMA OF THE PROSTATE.
The tissue is infiltrated with plasma cells due to the presence of a new growth. The central mass and the concentric deposition layers at the periphery of the body are well shown. × 600.

TECHNIQUE.—For microscopical examination, the tissue, either fresh or after preservation, should be cut into thin sections, and these deeply stained with 1 per cent. aqueous solution of methyl violet; the sections are washed in water and mounted in glycerin. The differentiation between the amyloid and other parts is more distinct if, after staining, the specimen be dipped for an instant in HCl and alcohol 1 : 100, and then carefully rinsed, before mounting in glycerin. The degenerated areas are thus stained rose-red, while the normal tissue elements have a bluish violet color. In some cases, for reasons which we do not know, the amyloid substance does not show a well-marked reaction with methyl violet. (Lugol's iodine solution stains fresh amyloid a mahogany brown color.)

[1] An extended study of amyloid degeneration may be found in a monograph by *Wichmann, G.* Zieglers Beitr., 1893, xiii, 487. See also *Schilder, P.*, ibid., 1909, xlvi, 602 (bibl.); *Davidsohn, W.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1908, xii, 424; *Hanssen*, Biochem. Ztschr., 1908, xiii, 185; and *Neuberg*, Verhandl. d. deutsch. path. Gesellsch., 1904, vii, 19.

A bibliography with a summary of experiments on the production of amyloid degeneration in animals will be found in an article by *Maximow, A.*, Virchows Arch., 1898, cliii, 353.

Corpora amylacea are small, spheroidal, homogeneous or lamellated bodies (Fig. 31) which occur in the acini of the prostate gland and in the ependyma of the brain and cord. In pathological conditions they are found in the lung (Fig. 32), in the brain and spinal cord, in extravasations of blood, and in various other situations. In the brain and cord they may be very abundant, both in the membranes and in the substance and also in the glial and ganglion cells. They occur rarely in the peripheral nerves. They may undergo calcification. When treated with aqueous iodine solution and dilute sulphuric acid, corpora amylacea assume a purplish color. With Best's method for staining glycogen they are colored a brilliant red, with Nile blue sulphate, a deep blue, and with

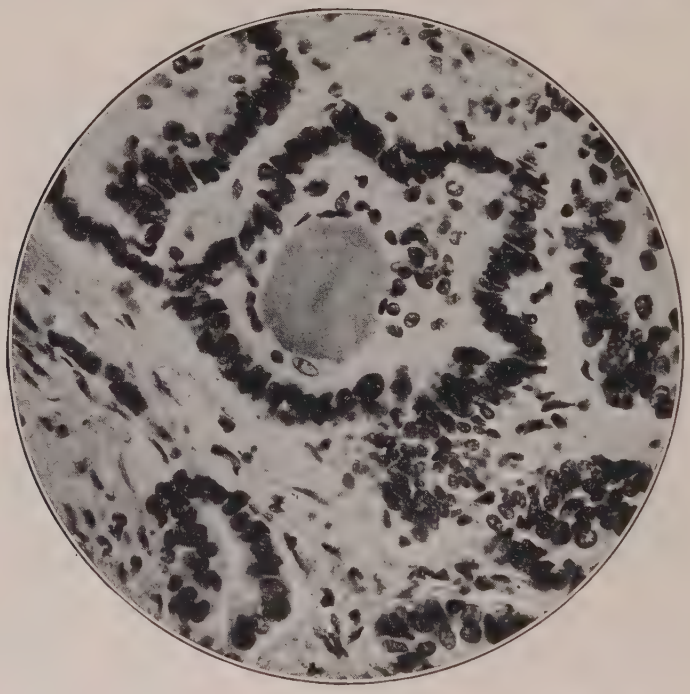


Fig. 32.—Corpus Amylaceum in Case of Carcinoma of the Lung.

neutral red, a deep red as are the fatty acids and soaps. It is probable, therefore, that they are composed of mixtures of some of the lipoids with glycogen or other carbohydrate material and traces of soaps and fatty acids. Corpora amylacea have no relation to amyloid degeneration.[1]

CALCAREOUS INFILTRATION.

There is in this condition a deposition, either in cells or in the intercellular substance, of larger and smaller granules composed chiefly of phosphate and carbonate of calcium (Fig. 33). These particles, when

[1] For a study of the relationship of corpora amylacea to amyloid substances, see *Ophüls, W.*, Jour. Exper. Med., 1900, v, 111 (bibl.). For a thorough study of corpora amylacea, especially those of the cerebrospinal axis, see *Stürmer, R.*, Nissl and Alzheimer, Histologische und histopathologische Arbeiten, Jena, 1913, v, 417 (bibl.).

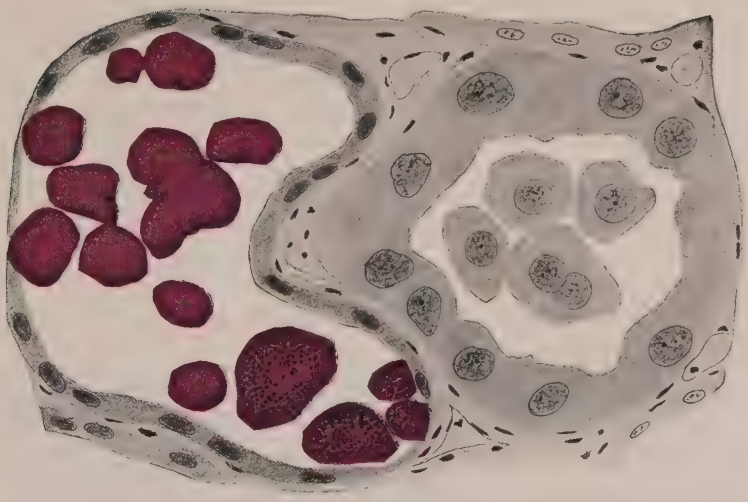


FIG. 33.—CALCIFICATION OF EPITHELIAL CELLS OF THE KIDNEY.

This is following sublimate poisoning. Some of the cells are converted into rounded, strongly refractile masses of lime salts. In others the lime is in the form of granules within the cells. The calcified parts are diffusely stained with hematoxylin.

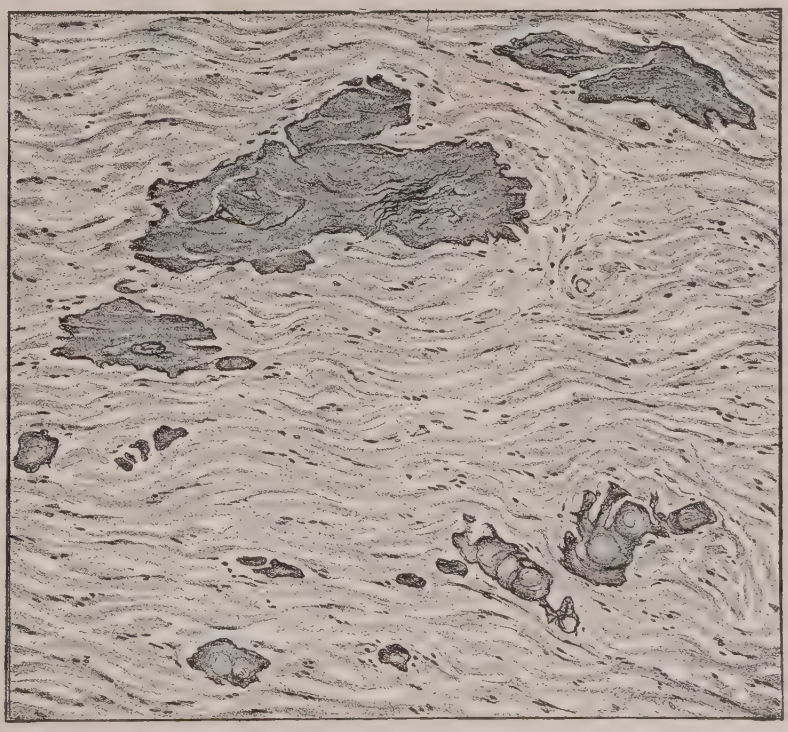


FIG. 34.—CALCIFICATION IN INFLAMED OMENTUM.

The lime salts have been deposited in areas where the fibrous tissue has become necrotic. The omental fat has disappeared.

abundant, give hardness, brittleness, and a whitish appearance to the affected tissue. Under the microscope they appear dark by transmitted, white and glistening by reflected, light. In hematoxylin-stained specimens, the tissue about the lime particles and masses is apt to be deeply and diffusely colored. Tissues may be nearly completely permeated with salts, or the latter may be scattered in patches through them (Fig. 34). Sometimes large lamellated concretions are formed in tissues, usually at the seat of some old inflammatory process. Calcium salts may be deposited under abnormal conditions either in tissues or in the retained secretions and excretions of the body. In pathological calcifications they are retained, not in the diffuse state in which they

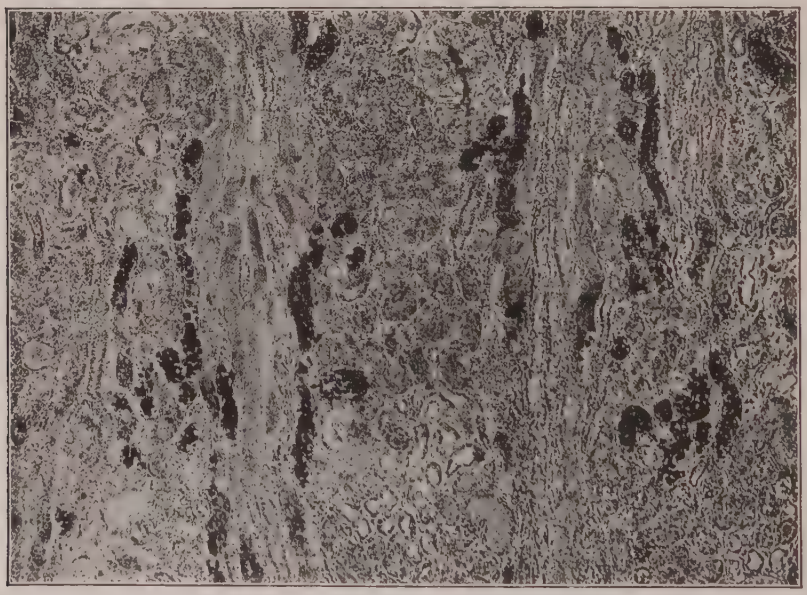


Fig. 35.—Calcareous Infiltration (Calcification) of the Kidney.
Following sublimate poisoning. The calcium salts are deposited chiefly in the necrotic and fatty epithelium of the terminal portion of the convoluted tubules.

exist in bone, but in particles or clumps, although the calcium compounds are essentially the same under both the normal and the pathological conditions.

Calcification in tissues usually, if not always, occurs in parts which are dead or are in a condition of reduced vitality as a result of some antecedent abnormal process, as a rule of an inflammatory nature. Fatty degeneration of cells frequently precedes calcification. Among the most common and important examples of calcareous degeneration may be mentioned those which occur in the valves of the heart in endocarditis and the walls of the blood-vessels in chronic obliterative endarteritis. It occurs in old thrombi, in old tuberculous areas, in old infarcts, in long-retained dead fetuses, in cartilage, in ganglion cells in old age

or after their death from any cause, and under many other conditions. Calcification of the epithelium and of casts in the kidney occurs after corrosive-sublimate poisoning in man (Fig. 35) and may be experimentally induced in animals. As examples of calcification of masses of secretion and excretion we may mention tonsillar calculi[1] in which masses of epithelial cells, bacteria, etc., are infiltrated with calcium salts. Of similar character are the preputial, bronchial, and intestinal calculi, and calculi in the ducts of various glands; and calcification in thrombi and other fibrinous structures.

The calcium salts are derived from the blood and lymph in which they are held in solution. The rationale of their deposition in damaged cells and tissues is not yet clear, though much work and discussion have centered in the problem. The presence of phosphorus in the affected areas; the existence of fatty acids in cells and tissues—since fatty degeneration so frequently precedes calcification—with which the calcium may form insoluble soaps; and proteins capable of uniting with calcium, have all been urged as determining factors. We cannot enter here upon a discussion of this point.[2]

Technique.—The carbonate of lime deposited in the tissues is dissolved by dilute acids with evolution of carbonic-acid gas. This process may be observed under the microscope by running 5 per cent. hydrochloric acid under the cover-glass upon unstained sections; the gas bubbles are caught as they evolve beneath the cover. If the salt is wholly calcium phosphate, the masses dissolve without gas production. If the fresh tissues are treated with silver nitrate solution, there is formed in the calcified areas a precipitate of silver phosphate which is blackened on exposure to light.

Pigmentation.

There is under normal conditions a certain amount of pigment in the body—in the rete Malpighii of the skin, in the eye, in muscle, and in fat. This pigment is elaborated by the body-cells and may vary considerably in amount.

The pigment which is formed under pathological conditions may be derived from the blood—*hematogenous;* from the bile—*hepatogenous;* or it may be elaborated by various cells after the analogy of the normal pigment—*metabolic.* Finally, pigment may be introduced into the body from without by drugs, in tattooing, or by inhalation—*extraneous.* The pigment in the body, of whatever origin, may be in yellow, brown, black, or reddish granules, or in crystalline form. It is often deposited in cells, but may lie free in the inter-

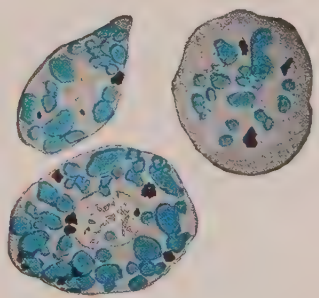


Fig. 36.—Pigment Containing Iron within Epithelial Cells of the Air Vesicles of the Lungs.

The iron pigment is colored blue. This specimen is from the lungs of an employé in the Subway in New York City.

[1] Calculi are masses of solid material of various composition precipitated from the body fluids. They will be considered under the separate organs in which they most frequently occur.

[2] Consult *Wells, H. G.,* Jour. Med. Research, 1906, N. S. ix, 491 (bibl.); Arch. Int. Med., 1911, vii, 721. Also, for a study of the rôle of diffusible soaps in the formation of cell fats and in calcareous degeneration, see *Klotz, O.,* Jour. Exper. Med., 1905, vii, 633, and 1906, viii, 322.

cellular substance. It is often transferred from place to place in the body.[1]

Hematogenous Pigment.—Blood pigment may form by the decomposition of hemoglobin in thrombi, or in extravasated or the circulating blood. Under these conditions the hemoglobin which is loosely associated with the plasma of the red blood-cells readily diffuses, leaving the cells—so-called "blood shadows"—pale and almost invisible and prone to disintegrate. This destruction of blood-cells is called *hemolysis*. Hemoglobin in solution in the body fluids[2] undergoes various phases of decomposition which we cannot follow in detail here. One of the derivatives or groups of derivatives of the hemoglobin is called *hemosiderin*.

Hemosiderin usually appears in the form of brown or black granules either in cells or free in the tissues. It is the usual form of blood pigment resulting from hemolysis. It gives the microchemical reaction for iron. For this test for iron in hemosiderin see foot-note below.[3]

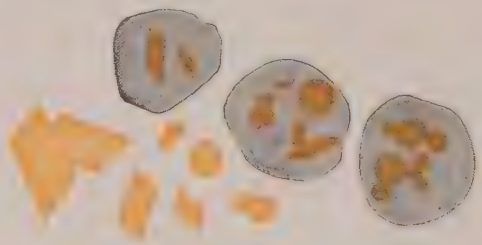


Fig. 37.—Hematogenous Pigment. Hematoidin Crystals and Masses Free and within Leucocytes.

A further common decomposition product of hemoglobin is *hematoidin*. Hematoidin is identical in chemical composition with the bile pigment, bilirubin. It may occur as red rhombic plates or acicular crystals or as granules (Fig. 37). It does not contain iron. This is the form of blood pigment which after a time is apt to form at the seat of old hemorrhages or in old blood-clots, thrombi, etc., where it may persist for a long time.

Red blood-corpuscles may be taken up by various forms of phagocytes, and within these cells the decomposition of the hemoglobin may lead to their pigmentation. Such cells are frequent in the pulmonary alveoli in chronic cardiac disease, as the so-called "heart failure cells."

Hemolysis may take place in the circulating blood in many forms

[1] See *Askanazy, M.*, Centralbl. f. allg. Path., 1906, xvii, 642.

[2] See page 520.

[3] To differentiate free iron and certain of the iron-containing pigments of the hemosiderin group, sections of the alcohol-hardened tissue are placed for an hour or longer in a 2 per cent. aqueous solution of ferrocyanide of potassium. Transfer to glycerin containing 0.5 per cent. hydrochloric acid. Under these conditions the iron will be stained blue or greenish-blue (Fig. 36). In order to secure a reaction for the ferrous as well as the ferric salts, use a mixture of 1 gram each of ferro- and ferricyanide of potassium in 100 c.c. of water. Transfer to acid glycerin as above. Contrast stains may be secured by alum carmine.

There are, it should be remembered, certain iron compounds—the so-called "masked" iron—which are not demonstrable by the ordinary reaction.

For a résumé of the microchemical reactions for iron, with bibl., see *Tracy, M.*, Jour. Med. Research, 1905, N. S. ix, 1; also, *Mann*, Physiological Histology, Oxford, 1912, p. 290.

of poisoning, in acute infections, notably in malaria, in pernicious anemia, in various cachexiæ, etc. The hemoglobin thus set free in the body fluids may be eliminated through the urine, inducing hemoglobinuria; it may be used by the liver in the formation of bile; or it may undergo decomposition, and its derivatives may be deposited in the cells of various organs and in the tissues as pigment granules.

A condition called *hemochromatosis* has been described, in which a brown pigment, probably derived from the hemoglobin of the blood, is deposited in various tissues of the body. The organs in this condition may appear notably pigmented on gross examination. The pigment particles which are found in the epithelial cells of glands, especially of the liver and pancreas, contain iron; while an iron-free pigment may be present in the smooth muscle cells of the gastrointestinal canal and of the blood- and lymph-vessels, and in connective-tissue cells. This pigmentation is commonly associated with cirrhosis of the liver. Hemochromatosis may be associated with diabetes mellitus and cirrhosis of the liver, together with pigmentation of the skin—"bronze skin." The conditions leading to hemochromatosis are still obscure.[1]

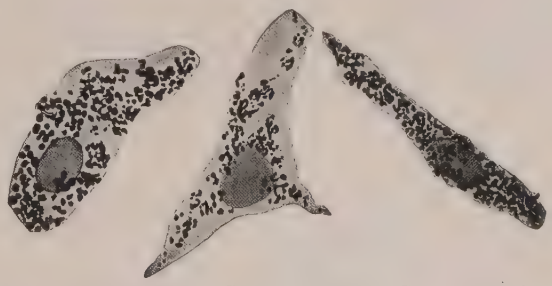


Fig. 38.—Anthracosis—Pigmentation of Connective-tissue Cells of the Lungs from Inhaled Coal Dust.

Hepatogenous Pigment.—Pigmentation of tissues from the bile occurs under various conditions. The bile may enter the blood and tissue fluids in obstruction of the gall-ducts by inflammation, tumors, calculi, etc. In the condition called *jaundice* or *icterus* the tissues are stained yellowish or yellowish-green by bile pigment. Icterus, it should be remembered, may also occur in infectious diseases and in toxemia, under conditions which lead to destruction of red blood-cells within the vessels. Bile may still be formed when the portal blood is prevented from reaching the liver.[2] Such transformation may take place, also, in the pleural and peritoneal cavities.[3] Even an excessive carbohydrate diet will increase the formation of bilirubin.[4] Bile pigment may be deposited in the liver, kidney, and elsewhere in the form of yellow or brown granules.[5]

It consists largely of *bilirubin*, a substance identical with hema-

[1] For a careful study of hemochromatosis, see *Opie, E. L.*, Jour. Exper. Med., 1899, iv, 279 (bibl.).
[2] *Whipple, G. H.*, and *Hooper, C. W.*, Jour. Exper. Med., 1913, xvii, 593, 612.
[3] *Hooper, C. W.*, and *Whipple, G. H.*, Jour. Exper. Med., 1916, xxiii, 137.
[4] *Hooper, C. W.*, and *Whipple, G. H.*, Am. Jour. Physiol., 1916, xl, 332, 349
[5] *Posselt, A.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1915, xvii², 719.

toidin, being derived from hemoglobin through the metabolism of the liver cells.

Ochronosis.—Under conditions which are as yet little understood, minute, iron-free, gray or black granules of pigment which may be called melanotic are deposited especially in cartilage but also in other connective tissues. Melanuria may accompany this form of tissue pigmentation. This condition has been called *ochronosis.*[1]

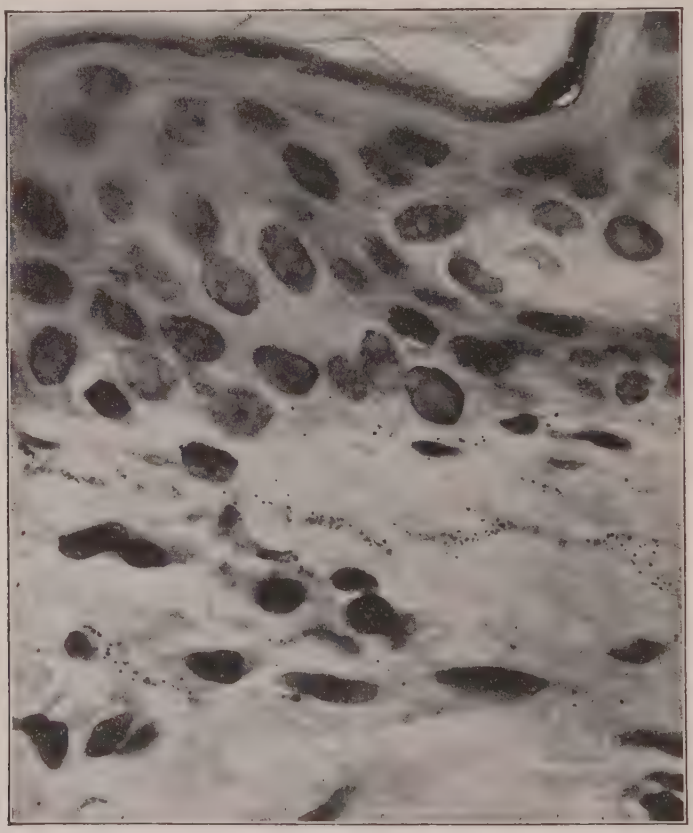


FIG. 39.—GENERALIZED ARGYRIA FOLLOWING USE OF ARGYROL.
The pigment may be seen lying in delicate strands in the connective tissue of the corium.

METABOLIC PIGMENT.—Pigments called *melanins,*[2] and probably derived from albumins, may be elaborated by various forms of cells, by processes apparently somewhat analogous with those concerned in normal pigmentation.[3] This is exemplified in melanotic tumors (Plate

[1] For a study of ochronosis see *Pick*, Berl. klin. Wchnschr., 1906, xliii, 473, 509, 556, 591; and *Poulsen*, Zieglers Beitr., 1910, xlviii, 437 (bibl.).

[2] *Wieting* and *Hamdi*, Zieglers Beitr., 1907, xlii, 23; *Smith, D. T.*, Bull. Johns Hopkins Hosp., 1920, xxxi, 239.

[3] For a study of the nature of skin pigment consult *Abel, J. J.*, and *Davis, W. S.*, Jour. Exper. Med., 1896, i, 361; *Chittenden* and *Albro*, Am. Jour. Physiol., 1899, ii, 291; also *Mann*, Chemistry of the Proteids, New York, 1906, p. 580.

For a general survey of such pigments, see *Hueck, W.*, Zieglers Beitr., 1912, liv, 68, and *Oberndorfer*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1921, xix[2], 47 (bibl.).

II), most frequently of the choroid and the skin, and possibly in the bronze skin of Addison's disease.

Pigment whose nature is not very clearly defined may form in the smooth muscle tissue of the gastrointestinal walls, in various cachexiæ, in the heart muscle, in the so-called "brown atrophy," and, under certain conditions, in the liver. In old age pigment is frequent in the ganglion cells. It may occur in the cervical sympathetic ganglion cells in exophthalmic goiter.[1]

Extraneous Pigment.—As examples of pigment introduced into the body from without, we may mention the deposition of minute particles of lead—*lead line on the gums*—or of silver from the use of silver salts —*argyria;* the coloring of the skin and lymph-nodes from tattooing; and especially the pigmentation of the lungs and bronchial glands from the inhalation of coal and other dust—*pneumonokoniosis* (Fig. 38). This is universally present under the conditions of indoor life which modern civilization imposes. Such pigment may be brown or black, and is usually in very small particles within cells or in the intercellular stroma.

The pigment in argyria may result from the ingestion of inorganic salts of silver or from the continued use of local applications of the organic compounds, such as argyrol. In the latter case, the subepithelial tissues of the entire body may contain enough pigment to give the patient a dusky bluish tint (Fig. 39). Local argyria is most often seen in the conjunctiva after the repeated employment of argyrol as an antiseptic.[2]

Necrosis.

Necrosis[3] is the death of a circumscribed portion of tissue in the living body. It may be the result of insufficient nutrition from cutting off the blood supply, as by embolism, thrombosis, ligature, pressure, etc., or it may depend upon the action of destructive chemical agents, extreme degrees of temperature, the Roentgen rays, and radium. It may be due to bacterial toxins or to toxins formed by the animal tissues; to nerve lesions leading to trophic disturbances; or to mechanical injury. Defective nutrition of the body in various acute and chronic diseases disposes the individual to local necrosis when subjected to any of the direct agencies just enumerated.

The general appearance of dead tissues varies greatly. In some cases there is a simple and gradual disintegration and softening of the tissue, resulting in a mass of degenerated cells and cell detritus, with more or less fluid and various chemical substances arising from decomposition. The softening of the brain in embolism is an example of simple necrotic softening—*liquefaction necrosis.* In some cases the dead tissues merely dry and shrivel gradually and become hard and dark-colored.

In another class of cases the dead tissues are permeated by fluids which may be dark red in color, from the solution of coloring matter

[1] *Wilson, L. B.*, Am. Jour. Med. Sc., 1916, cli, 809.
[2] *Olsen, G. M.*, Jour. Am. Med. Assn., 1917, lxix, 87.
[3] *Albrecht, E.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907, xi², 1123 (bibl.).

from the blood, and may contain bacteria which induce putrefaction, with the production of gases and various new chemical substances. The tissues become swollen and granular, and disintegrate; and finally the whole may form a mass of irregular granules, with fat droplets, tyrosin, leucin, and various forms of crystals, shreds of the more resistant kinds of tissue, and bacteria.

The death of cells is marked by cessation of function and by certain morphological and chemical alterations of the body and the nucleus. As a rule the highly specialized cells, such as the functional cells of the brain, liver, and kidney, are most vulnerable in the presence of harmful conditions.

There is at first no evident morphological difference between dead cells and living cells. But very soon in the former, changes occur. The cytoplasm may swell and become homogeneous from imbibition of fluids; or, on the other hand, it may become more coarsely granular. The nucleus stains less deeply or not at all with hematoxylin or other nuclear dyes (Fig. 40), owing to the disappearance of the chromatin which seems to dissolve in the tissue juices; this is called *karyolysis*. Sometimes, however, the chromatin does not dissolve, or only partially dis-

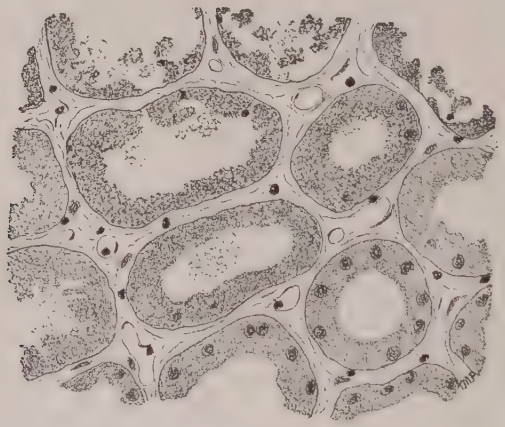


FIG. 40.—NECROSIS OF EPITHELIUM IN THE KIDNEY.
The cells in the lower portion of the cut are nearly normal; most of those above are more coarsely granular and have failed to take the nuclear stain, while at the top they are disintegrating.

appears, the remainder breaking up into irregular, more or less deeply staining granules. This is called *karyorrhexis*. The nuclei of cells which are undergoing regressive processes or dying may become smaller and denser than normal and stain more deeply; this is called *pycnosis*. Presently the cell body may contain fat droplets, or without this it may disintegrate.

GANGRENE.—When death of a considerable mass of tissue occurs, and this either dries, as is possible on the surface of the body, or is associated with putrefaction in the tissue, the condition is called *gangrene*. The involved part, when on the surface of the body, may dry and become

hard and brown or black—*mummification, or dry gangrene*[1] (Fig. 41). On the other hand it may, when putrefactive bacteria are present, in addition to its discoloration, become soft and infiltrated with foul-

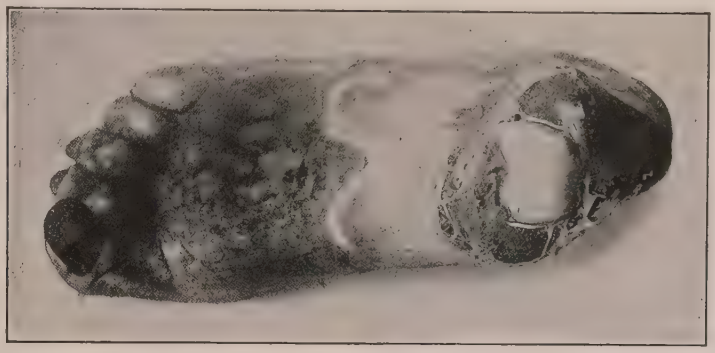


FIG. 41.—GANGRENE OF THE FOOT.
A sharp line separates the dead and gangrenous portion of the foot from the living tissues about the posterior part and the ankle.

smelling gases—*moist gangrene.* If the affected part be comparatively bloodless, the discoloration, which is largely due to decomposition of the blood pigment, may be absent.[2]

FOCAL NECROSIS.—Necrosis involving a small circumscribed area of tissue, such as is frequent in toxemia, is called *focal necrosis* (page 238). Whether such focal necroses are due to destruction of the capillaries by the toxins in the blood, to a primary lesion of the parenchyma cells, or to minute thrombi, is as yet undetermined.

ULCERATION.—Necrosis with erosion involving the surface of the skin or of the mucous or serous membranes is called an *ulcer.* An ulcer may be necrotic in origin, from the cutting off of nutrition in a circumscribed area, as in some forms of gastric ulcer. This may be associated with reactive inflammatory processes which tend to promote repair. On the other hand, the process may be inflammatory in origin, death of tissue following; a good example of this is the typhoid ulceration of the intestine which begins as an inflammatory process in the Peyer's patches.

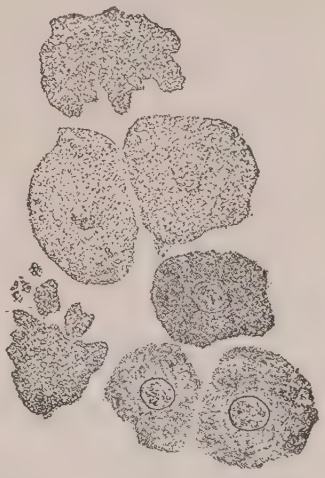


FIG. 42.—COAGULATION NECROSIS IN CELLS.
The disappearance of the chromatin from the nuclei is indicated by their failure to stain, especially marked in the upper cells.

COAGULATION NECROSIS.—If dead areas of tissue (whether this condition be due to mechanical injury, to disturbances of nutrition, or to

[1] For a study of senile gangrene, see *Falta,* Ztschr. f. Heilk., 1899, xx, 393 (bibl.).
[2] For more detailed studies of gangrene consult works on surgery.

the local action of bacterial or other poisons) contain the substances necessary for the coagulation of their albuminous constituents, or if they are bathed with body fluids from adjacent parts in which the circulation is maintained, a characteristic coagulation of the necrotic elements is apt to occur. The composition of the cells of the tissue is altered, so that the cell bodies are shining and translucent, sometimes altered in shape; while the chromatin and finally the nuclei of the cells disappear (Fig. 42). The white infarctions of the spleen and kidneys, the areas of coagulation necrosis in tuberculosis, and the pellicle in croupous inflammation of the mucous membranes are the most common examples of this lesion.

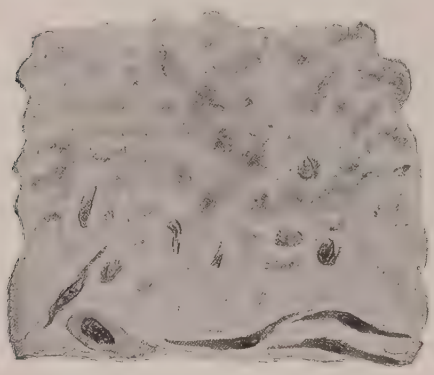


Fig. 43.—Coagulation Necrosis. In tuberculous tissue.

If, for example, in the spleen, one of the small arteries is plugged by an embolus, a corresponding portion of the spleen becomes anemic and appears as a white, wedge-shaped mass, sharply defined from the surrounding splenic tissue. If such a white infarction has existed but a short time, there is hardly any difference between the appearance of its anatomical elements and those of the surrounding spleen, except that they are differently affected by staining-fluids. If the infarction is older, the cells are small and shiny and their nuclei cannot be seen.

In croupous inflammations of mucous membranes the epithelial cells become shiny, the nuclei disappear, and the shape of the cells is changed by the coagulation necrosis, so that a number of them together often look like a network of coagulated fibrin.

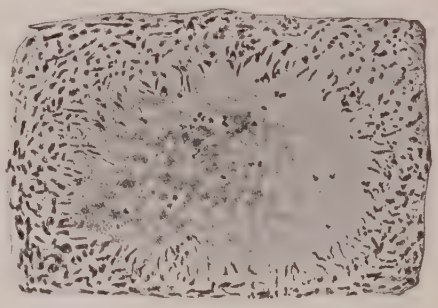


Fig. 44.—An Area of Cheesy Degeneration (Caseation) in a Miliary Tubercle in the Lungs.

Cheesy Degeneration (*Caseation*). —As commonly used, this term embraces the changes in the tissues which we have just considered under the more appropriate name of coagulation necrosis. But it is also applied to that form of degeneration in which, under a variety of conditions, the dead tissue elements lose their normal structural features and become converted into an irregularly granular albuminous and fatty material (Fig. 43 and 44), which sometimes tends to disintegrate and soften, sometimes dries and becomes dense and firm, or may become infiltrated with salts of calcium. Thus cheesy degeneration may, and very often does, occur in tissues which are in the condi-

tion of coagulation necrosis; but it also occurs in tissues which are not the seat of coagulation necrosis, but which, for a variety of reasons and in a variety of ways, have lost their vitality.

The terms "coagulation necrosis" and "cheesy degeneration," as commonly used, in part actually cover the same degenerative conditions. Both are most frequently seen in connection with tuberculous infections. While their exact nature is as yet somewhat obscure, a step toward the understanding of the chemical processes underlying this type of necrosis has been made.[1] The older theory was that caseation was produced by the anemia, the tissues being practically avascular. The more prevalent view is, however, that the tubercle bacillus contains toxins which destroy the tissues, though an explanation for the persistence of the cheesy areas has been lacking. Recent work has shown, however, that the tubercle bacilli contain a ferment-inhibiting substance which seems to be of a fatty-acid nature and when saponified has the power of inhibiting the action of the autolytic, tryptic, and leucoproteic ferments; thus, the toxic substances of the tubercle bacilli have free play in causing necrosis of the tissues. This necrotic material is not removed by the ordinary process of autolysis or phagocytosis because of the inhibiting substances of the tubercle bacillus. The anemia caused by the occlusion of the blood-vessels also plays an important part as the cutting off of the fluid supply from the tissues prevents the dilution and subsequent absorption of the inhibiting substance. The reaction at the periphery of the cheesy area also prevents the entrance of fluids and thus the caseous area gradually increases in size, as the bacterial toxins cause the death of the surrounding tissues. The administration of iodides which saturate the fatty acids and prevent them from inhibiting the ferment often leads to breaking down of the cheesy areas in tuberculosis and even more strikingly in syphilitic gummata.

Fat Necrosis.—This is a degenerative process most frequent in the subperitoneal fat and in and about the pancreas, and especially associated with lesions of that organ. We refer for details to the special section (page 814).

The Disposal of Necrotic Tissues.—Necrotic tissues may be separated from the living body by inflammatory processes and wholly cast off, as in gangrene of a limb, or in bone, the dead portion in this case being called a *sequestrum*.

Fragments of dead cells and tissues in the living body are in part disposed of by leucocytes or other mesoblastic cells which may be attracted to them, and may cause their solution by proteolytic enzymes which are set free or by the incorporation of particles of the dead tissue into their bodies where they are destroyed.[2]

Furthermore, the absorption of necrotic tissues is in part due to proteolytic enzymes furnished by the dead and degenerating cells themselves. The self-destruction of tissues in the ways indicated is called *autolysis* (page 126). To what extent the lytic substances through

[1] *Jobling, J. W.*, and *Petersen, W.*, Jour. Exper. Med., 1914, xix, 251, 383.
[2] See Phagocytes, p. 118.

which dead tissues are softened may be derived directly from the blood plasma is not yet clear. At any rate, through chemotaxis, phagocytosis, and autolysis considerable masses of necrotic tissue may be finally removed.[1] Dead bone is dissolved and disposed of by special forms of cells called *osteoclasts*[2] (page 123).

Recent studies relating to the adaptation of the body to various alien substances have led to new conceptions of the nature of the processes by which the body frees itself of useless or harmful material either developed within it or introduced from without. (For a fuller consideration of these processes see *cytolysis*, page 203).

[1] *Wells, H. G.*, Jour. Med. Research, 1906, N. S. x, 149.
[2] *Arey, L. B.*, Anat. Rec., 1917, xiii, 269.

CHAPTER IV.

PROGRESSIVE TISSUE CHANGES.

Hypertrophy and Hyperplasia.

HYPERTROPHY.—Under a variety of conditions, cells, parts of the body, or even organs become larger than normal. The structural change to which this enlargement is due may be a simple increase in size of the elementary structures of the part, the cells. This is called *simple hypertrophy*. It is usually associated with some increased functional demand upon the cells and an increase in their functional capacity; as, for example, in the hypertrophy of the heart with lesions of the valves, or in the hypertrophy of one kidney, which in case of diminution or suspension of function in the other assumes the work of both—*compensatory hypertrophy*.[1]

Pathological hypertrophy in response to functional demand—*functional hypertrophy*—has its physiological prototype in the changes in the uterus and in the mammary gland during pregnancy.

It should be borne in mind that the simple enlargement of a part or organ does not necessarily involve the hypertrophy of any of its structural elements. Thus there may be an increase of fat in a muscle causing its enlargement; waxy degeneration of the liver may determine great increase in the size of this organ. It is well to limit one's conception of hypertrophy to enlargement of specific structural elements of a part with maintenance or increase of functional capacity, and to consider other instances of enlargement, such as those just cited, as examples of *pseudohypertrophy*.

HYPERPLASIA.—In many cases the increase in size of a part or organ is due not only, or not at all, to the increase in size of its elementary structures, but to an increase in their number. This increase in number of the structural elements of a tissue or organ is called numerical hypertrophy, or *hyperplasia*.[2]

Hyperplasia of connective tissue is of frequent occurrence in association with atrophy of the parenchyma of various organs, replacing the damaged cells as these diminish or disappear. This is called *replacement hyperplasia*.

Hypertrophy and Hyperplasia in Special Organs.—In hypertrophy of the *heart* associated with the increased amount of work which it has to do in maintaining the circulation in various forms of valvular lesion,

[1] For bibliography of compensatory hypertrophy, see *Aschoff*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 67.

[2] Consult for examples of hyperplasia and hypertrophy the following sections on Regeneration and Inflammation.

pulmonary and vascular obstruction, or excessive bodily strain;[1] in hypertrophy of the unstriated muscle such as may occur in the bladder in urethral stricture, calculi, etc., in the stomach in pyloric stenosis, in the arteries in chronic diffuse nephritis; as well as in the voluntary-muscle hypertrophy from athletic exercises, etc., the individual muscle cells and fibers are increased in length and in thickness.

In hypertrophy of one *kidney* from the loss of the other or of part of its own substance by operation or lesion, there is enlargement of the epithelium, especially of the convoluted tubules and of the glomerular epithelium covering the tuft, the latter being also enlarged. Changes in the collecting tubes and in the interstitial tissue are less marked even in kidneys which are greatly increased in size.

Compensatory hypertrophy of the *liver* following destruction of part of the parenchyma seems to be largely due to the new-formed liver cells, and to hyperplasia of the interstitial tissue, but the hypertrophy of the old cells occurs.

Compensatory hypertrophy of the *thyroid*[2] and *adrenals* has been experimentally induced. Hypertrophy of one *testicle* occurs after the removal of the other, and the same is true of the *mammary gland.* Compensatory hypertrophy of the *ovaries* has not been observed.

After destructive injury to the *spleen* its function may be in a measure assumed by the bone-marrow and lymphatic tissue which undergo compensatory hypertrophy.

In most of these conditions hyperplasia of the interstitial tissue is associated with the hypertrophy of the specific parenchyma cells whose response to increased functional demands is marked by simple hypertrophy.

Metaplasia.

In the development of the body there is a constant and progressive differentiation of cells. When development is complete a certain specificity exists, marked by functional and structural characters. These specific characters in cells are fairly permanent under normal conditions. Under a variety of abnormal conditions, however, they may undergo modification so that one type of cell or tissue may assume more or less completely the characters of another type. But the limitations of this change in type are strictly drawn, so that one type can assume only the characters of another which is closely related to it. This change of one form of tissue into another is called *metaplasia.*

Thus, by a gradual change in the cells and stroma of fibrous tissue, this may be converted into bone, as mucous tissue may become fat tissue, and hyaline cartilage become fibrous. Metaplasia is a process involving active changes on the part of the living cells of the tissue, and should be clearly distinguished from certain degenerative and infiltrative processes, in the course of which one form of connective tissue may assume super-

[1] For conditions of cardiac hypertrophy see page 636. For a fuller consideration of the phases and conditions of hypertrophy see *Adami*, Principles of Pathology, Philadelphia, 1908, vol. i, 535.

[2] Such hypertrophy is not constant after removal of portions of the gland, and the conditions under which it may occur must be considered at present as not accurately determined. See for discussion of the matter, *Halsted, W. S.*, Am. Jour. Med. Sc., 1914, cxlvii, 56; and *Hunnicutt, J. A.*, ibid., 1914, cxlviii, 207.

ficial resemblances to others of the group, as in calcareous and mucoid degeneration.

The infiltration of the cells of fibrillar connective tissue with fat, and the reverse process in which the fat is lost, as in atrophy and emaciation, are not, strictly speaking, examples of metaplasia.

While metaplasia is most common among the members of the connective-tissue group, it sometimes occurs in other tissues. Thus, for example, the epithelium of the nose, bronchi, urinary passages, corpus and cervix uteri, and gall-bladder may under a variety of conditions assume the characters of squamous epithelium of the skin type.[1]

One should be critical in estimating the value of evidences of metaplasia, which has apparently been assumed to occur more frequently than the facts justify. For example, many instances of alleged metaplasia can be equally well accounted for on the assumption of defects of development in which a certain portion of tissue has failed to complete its differentiation, thus remaining in form and in situations which simulate the results of metaplasia. Or, cells of the differing types may have grown into the region from adjacent parts.

When differentiation has advanced so that such distinct types of tissue have been formed as connective tissue, epithelium, muscle, nerve, these do not again merge through metaplasia. There is no evidence that mesoblastic tissues can be converted into those of the epiblastic or hypoblastic type or vice versa.

Reversion.

Under various conditions, but especially when highly differentiated cells have been thrown out of function, often as the result of inflammatory processes, they appear to assume the morphological characters which belong to an early stage in their development. This is called *reversion*, *reversionary metamorphosis*, or *kataplasia*. Thus the flat epithelium of the air vesicles of the lungs or the cylindrical epithelium lining the bronchi or the stomach may become cuboidal. In the kidney the epithelium of the glomeruli and also of the convoluted tubules may become cuboidal. So in chronic peritonitis the mesothelium may become greatly thickened. Muscle fibers and connective-tissue cells may assume for a longer or shorter period distinctly embryonic forms. But here, as in metaplasia, one should accept the morphological evidence of reversion with due reserve, since in many instances the cells of the lower type in question may be the results of a reparative process not yet complete, and may have been derived from newly formed cells.[2] Furthermore the shape of cells in general is so closely dependent upon nutrition, pressure, and mutual relationship that even slight departures from these may lead to changes in form quite as marked but not of such significance as those involved in reversion.

[1] For references to epithelial metaplasia, see *Menetrier*, Bouchard's Traité de pathologie générale, iii, pt. 2, p. 784. For a discussion of metaplasia, see *Ribbert, H.*, Lehrbuch d. allg. Pathologie, 5th edition, Leipzig, 1915, p. 174; and Geschwulstlehre, 2d edition, Bonn, 1914; also *Adami, J. G.*, Principles of Pathology, Philadelphia, 1908, vol. i, 586.

[2] See *Ribbert, H.*, Geschwulstlehre, 2d edition, Bonn, 1914; also, for general review of reversion and growth in tissues, *Adami, J. G.*, A. Jacobi Festschrift, 1900, p. 422; and Principles of Pathology, Philadelphia, 1908, vol. i, 810.

Regeneration.

General Considerations.—It is during the earlier periods of life that the new formation of cells in the body is most active. From the fertilization of the ovum until the tissues and organs have assumed the varied forms and functions which the physiological division of labor among the cells imposes, cell proliferation and cell adaptation to a changing environment are constant and important features of individual development. After this time, under normal conditions, new cell formation is largely limited to the replacement of worn-out cells or to the restitution of such cells as may be sacrificed in the performance of their physiological functions.

The studies of Bizzozero have shown that, notwithstanding the great diversity in the capacity for physiological regeneration among tissues, they may be conveniently grouped into three classes, as follows: *First*, tissues whose cells are capable of multiplication throughout the life of the individual or for a considerable period after maturity, and so lead to a continual regeneration. These are tissues whose cells are labile and evanescent. In this class are the parenchyma cells of those glands or structures which produce formed elements, such as the spleen, lymph-nodes, bone-marrow, ovary, testicle; also the epithelium of the skin with its hair follicles and sebaceous glands, and of the mucous membranes of the respiratory, digestive, and genitourinary organs. *Second*, tissues whose elements increase by division up to the time of birth, or sometimes for a short period thereafter, when evidence of physiological regeneration ceases. These are tissues with permanent cells. In this class are the parenchyma cells of those glands which secrete fluid material, such as the liver, kidney, pancreas, salivary glands, etc., also members of the connective-tissue group, fibrous tissue, cartilage and bone, and the smooth muscle fibers. *Third*, striated muscle and nerve tissue. In these tissues, division by mitosis ceases at an early period and before the tissues have acquired their special characters. Here extensive regeneration does not occur.

This grouping of tissues in accordance with their capacity for physiological regeneration, while liable to modification under further research, affords a suggestive guide in our studies of regeneration under abnormal conditions. For beyond the regenerative capacity normally exercised by cells in response to the physiological wear and tear of life, they are frequently called upon to make good unusual losses, as the result of many forms of injury.

Regeneration of injured tissues and new growths, as well as the hyperplasias above mentioned, are invariably brought about by proliferation or other changes in living cells. Furthermore, just as the cells of the adult organism are the offspring of one original cell, the ovum, so are all the new cells which appear in the body under abnormal conditions derived from pre-existing cells by division.

We shall now briefly summarize the morphological changes which cells undergo in division and shall then indicate the degree of regenerative capacity which various forms of tissues possess.[1]

STRUCTURE OF CELL AND MODES OF DIVISION.

The careful and minute study of cells during the act of division, which has been recently made, has revealed many most curious phenomena and has opened a new world of observation nearer to the elementary expression of life than had seemed possible in earlier times. It will

[1] For a summary of much of our knowledge of regeneration, see *Marchand, F.*, Process der Wundheilung, Stuttgart, 1901.

suffice for our purpose briefly to indicate some of the more striking features of the new cell lore.

It is well to recall at the outset that recent studies of cells have shown that even in their simplest forms they are highly organized, and that their different parts have special functions to perform. Thus the nucleus presides over the constructive metabolism or assimilative process of the cell and furnishes the physical basis upon which the transmission of hereditary characters depends. The cytoplasm of the body, on the other hand, is concerned in those phases of metabolism which result in the liberation of energy in movements of various kinds and in the formation of new chemical substances. The centrosome also in certain cells, though not apparently in all, appears to play an important part in the changes incident to division.

In addition to the nucleus and its chromatin network, which with the central bodies and the attraction spheres play so important a part in the mechanism of cell fertilization and division, there are other constituents of the cell—the *mitochondria*[1] and the *plasmosomes*—of which less is known. Besides these, many of the highly specialized cells carry specific granules, probably in many instances connected with the limited functional activity to which the cell is dedicated, for example, the Nissl granules of the nerve cell, the secretory granules of the salivary and pancreatic organs, and the neutrophile and eosinophile granules of the leucocytes. These characteristic aggregates of cytoplasmic protoplasm are present chiefly at the full functional maturity of the cell, while the mitochondria and plasmosomes are abundant in practically all embryonic tissue elements, including the sex cells, the blood, and the ganglion cells. They can be seen in unstained preparations and take up certain of the so-called vital stains, as, for example, Janus green.[2]

In the process of fertilization, the mitochondria mingle and, it is thought by some, fuse as do the chromosomes. Apparently they arise in the cytoplasm and are connected with its metabolic processes, as they may disappear during great functional activity; but their relationship to the various morphological products of such activity is not yet clear. In tumor cells they may be absent or very scanty, an evidence that such cells are not truly "embryonic," as is so often stated.[3]

The plasmosomes are structures which give rise to the granules characterizing many of the cells. They are genetically related probably to the secretion granules, the fat and glycogen deposits, and the various pigments which occur in cells.[4] The Golgi apparatus is another peculiar structure present in the cytoplasm.[5]

[1] Synonyms: Chondriosomes, chondrioconts, chondriomes, cytomicrosomes, chondriomites, electosomes, plastosomes, Altmann's granules, etc.

[2] *Lewis* and *Lewis*, Am. Jour. Anat., 1914-15, xvii, 340 (bibl.); *Cowdry, E. V.*, Am. Jour. Anat., 1916, xix, 423 (bibl.) and The mitochondrial constituents of photoplasm, Contrib. Embryol., Carnegie Inst., Washington, 1918, viii, 39 (bibl.).

[3] *Altmann*, Die Elementarorganismen, 2d edition, Leipzig, 1894; *Barratt*, Quart. Jour. Med. Sc., 1913, lviii, 553; *Beckton*, Arch, Middlesex Hosp., 1910, xix, 103, 111, 115; *Benda*, Verhandl. d. deutsch. path. Gesellsch., 1914, xvii, 5 (bibl.); *Porcelli-Titone*, Zieglers Beitr., 1914, lviii, 237; *Meves*, Arch. f. mikros. Anat., 1908, lxxii, 816.

[4] *Benda*, Verhandl. d. deutsch. path. Gesellsch., 1914, xvii, 5 (bibl.); *Arnold*, Anat. Anz., 1913, xliii, 433; *Duesberg*, Ergebn. d. Anat. u. Entwick., 1911–12, xx, ii, 567.

[5] *Da Fano, C.*, Seventh Sci. Report, Imperial Cancer Research Fund, London, 1921, p. 67.

Besides the granules which occur in the cells, there are in many types fine anastomosing canaliculi demonstrable by special means. They have been described in the nerve cells, in glandular and columnar epithelium, and as especially well marked in the liver cells, and have been thought to afford means for the interchanges of fluids between the cell and the circulation.[1]

In addition to these morphological elements, cells contain ferments which enable them to alter absorbed food materials, and either use them directly, as is the case with sugar, or store them in altered form, as with the proteins or their elements, the amino-acids. The number and capacity of these ferments vary greatly according to the cell. At least twelve have been identified in the liver cell. With the exception of the oxidase ferment found principally in the granular leucocytes, none can be easily demonstrated morphologically.

Two modes of cell division are commonly recognized. First, *indirect division* (mitosis, or karyokinesis); second, *direct division* (amitosis).[2]

Indirect (Mitotic) Cell Division.

This is the most common mode of cell division and is especially characteristic of embryonic cells and those which are undergoing active development. While it presents great variations, its general features may be thus briefly summarized:

Among the earlier changes which are to be seen in a cell about to divide by mitosis are a condensation and an increase in the staining capacity of the chromatin of the intranuclear network. This chromatin substance gathers into a contorted thread or threads, called the *spiremes* (Fig. 45, 2), within the nucleus, whose membrane with the nucleolus gradually disappears so that the spireme lies free in the cytoplasm; and at the same time with, or preceding, these changes in the nucleus, there may be a division of the centrosome when this is present, the segments resulting from this division passing to opposite parts of the cell, usually outside the limits of the nucleus. Around each of the new centrosomes, which stain deeply with hematoxylin or other nuclear dyes, may be a clear zone of unstained material, or a series of fine radiating fibrils, or both; the whole forming a structure called a *polar body* (Fig. 45, 2 and 3).

Now the threads of the spireme break across transversely, forming a series of more or less rod-like bodies called *chromosomes*, which form a somewhat flattened cluster or wreath between the polar bodies, lying in a plane at a right angle to a line passing between the latter. While this mass of chromosomes—sometimes called the *monaster*—has a stellar or wreath-like appearance when seen from the side, it is more band-like when viewed in profile (Fig. 45, 3 and 4).

Between the polar bodies and across the monaster there may now be

[1] See, for bibl., *Schäfer*, Quain's Anatomy, London, 1912, vol. ii, part 1, 25.

[2] For a general review of the theories of the mechanism of mitosis, see *Meek*, Quart. Jour. Med. Sc., 1913, lviii, 567; *Schäfer*, Quain's Anatomy, London, 1912, vol. ii, part 1, p. 25; and *Heidenhain*, Plasma u. Zelle, Jena, 1907. For interesting results of the imitation of mitosis by diffusion of chemicals, see *Leduc*, La biologie synthetique, Paris, 1912.

stretched a bridge or spindle of delicate fibrils resembling those about the centrosome in the polar bodies.

This fibril-spindle, together with the polar bodies, is called the *achromatic figure* in distinction to the structure formed from the chromatin, which stains with nuclear dyes, and is called the *chromatic figure.*

The whole complicated structure composed of both the chromatic and achromatic substance constitutes the *mitotic figure.*

Now each chromosome splits lengthwise into exactly equal parts. These parts separate into groups which pass to the polar bodies at opposite ends of the spindle. This is sometimes called the *diaster phase* of mitosis (Fig. 45, 5 and 6).

Corresponding to the division of the chromosomes into equal parts, the cell body divides, each part containing one of the groups of daughter chromosomes or diasters, together with one polar body and a part of the achromatic spindle (Fig. 45, 6). Now a new nucleus is formed

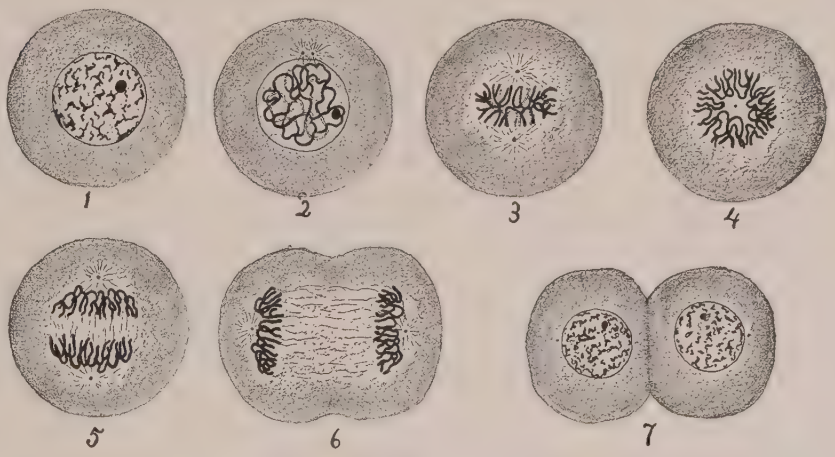


FIG. 45.—PHASES OF MITOSIS.

1. Resting cell. 2. Spireme phase: the centrosome has divided, the polar body is seen above, the nuclear membrane has not yet disappeared. 3. Monaster phase: the polar bodies have arranged themselves on either side of the monaster, here seen from the edge. 4. The monaster seen from the side. 5 and 6. Diaster phase: the chromosome clusters have separated and the achromatic figure is seen. In 6 the segmentation of the cell body has begun. 7. The completion of the nuclear division and segmentation of the cell body.

about the daughter chromosomes which gradually assume the characters of the resting intranuclear network (Fig. 45, 7). The achromatic fibrils disappear from the new cell, while the centrosome may also disappear or may take its place in the cytoplasm beside the new nucleus. The number of chromosomes in different species is extremely variable. In the worm *Ascaris megalocephala*, there are four; in the fruit-fly *Drosophila*, which has been the subject of a remarkable series of studies in heredity, there are four pairs of chromosomes, three large and one small; in many plants there is a slightly larger number; while in man there are probably forty-eight in the somatic cells of the female and forty-seven in those of the male.[1] In the spermatogonia of man there are forty-seven chromo-

[1] *Winiwarter, H.*, Études sur les spermatogenése humain, Arch. de biol., 1912, xxvii, 91.

somes which reduce to twenty-three pairs, leaving the x or sex chromosome unpaired. When the reduction division is completed, the x chromosome remains in one cell, consequently spermatozoa are of two kinds, one containing twenty-four, the other twenty-three chromosomes. These numbers, however, are not finally accepted,[1] for the technical difficulties in the study of the minute and interwoven structures are very great.

There are countless other variations and details in the minute processes of mitotic cell division and much interesting conjecture as to the meaning of the various changes in mitosis, which the scope of this work does not permit us to consider. But the facts already at hand are of extreme significance to the biologist and point toward large fields of research in pathology when the normal processes shall have been more clearly and exhaustively determined. What may be called a biological analysis of the results of mitotic division has yielded facts of great interest. As a result of Mendel's discovery of the unit or factorial type of heredity, the attention of biologists has been more and more focussed on the correlation between the appearance in the offspring of these segregated factors and certain structural details of the chromosomes. It is apparent that each chromosome of the egg and sperm has a constant regional distribution in its structure of the elements which carry these factors into the next generation. It has been possible to predict, from a knowledge of the position of these factors, a new combination of qualities in certain artificially bred strains which have not been hitherto observed in nature.[2]

Abnormal phases of mitosis are not infrequent. Thus, the mitotic figures may be asymmetrical, so that the distribution of chromatin substance to the daughter cells may be unequal (Fig. 46). There may be multipolar mitosis, so that, instead of two, several nuclei may form. Or, the new-formed chromosome masses may fail to share in the formation of the new nuclei.

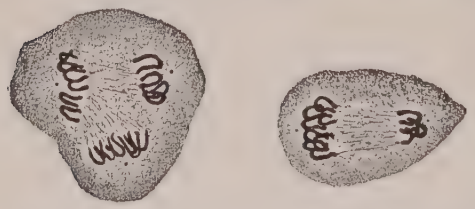


Fig. 46.—Abnormal Phases of Mitosis.
In both cells the mitosis is asymmetrical, and in the cell to the left tripolar.

Such abnormal mitoses are frequent in certain tumors, and they may be experimentally induced by the application of various chemical substances to living cells.[3] Too little is known about the conditions under which abnormal mitoses occur, and too little about the nature of the impulse to cell division in general, to justify to-day far-reaching conclusions as to the significance of these interesting abnormalities in the life of the cell.

The Significance of Mitosis.—The term *mitosis* or *karyomitosis* is applied to this indirect mode of cell division, on account of the involvement of the nuclear threads. It is also sometimes designated as *karyo-*

[1] *Guyer*, Accessory Chromosomes in Man, Biol. Bull., 1910, xix, 219; *Montgomery*, Jour. Acad. Nat. Sc., Philadelphia, 1912, xv, 1.

[2] For an interesting résumé of one phase of this work, see *Morgan, T. H.*, The Mechanism of Mendelian Heredity, New York, 1915.

[3] See *Klemensiewicz*, Zieglers Beitr., 1903, xxxiii, 51.

kinesis, from the form changes which these threads undergo. Aside from its intrinsic biological interest, a knowledge of mitosis in proliferating cells is of importance in pathology, because the recognition of mitotic figures often enables us to decide with certainty what particular cells or cell groups are involved in the formation of new tissue. The most significant feature, however, of the whole process of mitosis, with all its intricate variations, appears to be that the chromosomes, during their separation into two or more clusters to form the basis of new cells, undergo an exact longitudinal division. So that, under normal conditions, no matter how unequal the division of the cytoplasm may be, all of the new nuclei share alike in the chromatin substance of the parent nucleus. This fact appears to be of extreme importance in the recognition of a physical basis of inheritance.[1]

Direct (Amitotic) Cell Division.

In this, which although relatively rare, appears to be the most simple mode of cell division, without those preliminary changes in the nucleus which are seen in the mitotic cell division, the nucleus with its membrane becomes constricted and finally divides into two or more parts which become new nuclei. At the same time or following this simple nuclear division the cell body divides, and thus two or more cells may form in the place of one. If the nuclear division is not followed by that of the cell body, multinuclear cells, or "giant cells," may be formed.

The significance of the difference between the amitotic and the mitotic cell division is that, while in the former there is an exactly even division of chromatin to the daughter nuclei, the division in the latter is of the nuclear mass as a whole.[2]

It has been claimed that amitotic division occurs in leucocytes, in some forms of epithelium, and in the cells of neoplasms; and its occurrence has been described also in the cells of many vertebrates and of some of the lower aquatic forms. But there has recently been a change of opinion as to the nature of the process. While it is not denied that amitotic division of the nucleus may occur, recent opinion considers that there is no subsequent division of the cell body and that, therefore, the amitotic division of the nucleus is an entirely different process from the mitotic form.[3] After amitotic division of the chromatin material in the cell, mitotic division may occur in the separated basochromatic masses or karyomeres. It has been thought, also, that these karyomeres may, when the cell actually divides, combine and furnish the usual number of chromosomes, which then unite in a single spindle and divide in a typical manner.[4] Amitosis, therefore, according to these views,

[1] See summary by *Wilson, E. B.*, Science, 1913, N. S. xxxvii, 814; see also *Conklin, E. G.*, Heredity and Environment, Princeton, 1915. For a résumé of physiology and pathology of the nucleus see *Adami*, Brit. Med. Jour., 1906, ii, 1760; Principles of Pathology, Philadelphia, 1908, i. See also in this connection *Boveri*, Entstehung maligner Tumoren, Jena, 1914.

[2] For a comprehensive summary of facts and theories concerning the cell, both in higher and lower forms of life, consult *E. B. Wilson's* masterly work, The Cell in Development and Heredity, 3d edition, New York, 1925.

[3] *Macklin, C. C.*, Biological Bull., 1916, xxx, 445.

[4] For an excellent résumé of current views on amitosis, see *Conklin, E. G.*, Biological Bull., 1917, xxxiii, 396.

is not to be considered a genuine divisional phenomenon, but merely a means of increasing the nuclear surface and of distributing nuclear material throughout the cell. Thus, it is comparable to the phenomenon of lobulation, fragmentation, or distribution of the nucleus, so familiar to students of hematopoietic cytology.

GENERAL CHARACTERS AND LIMITATIONS OF CELL REGENERATION.

It should be borne in mind, in studying the regeneration of various kinds of cells and tissues, that the acquirement by certain cells of special functional powers as the result of the physiological division of labor has involved the impairment of some of their more primitive general capacities, among these that of reproduction. Thus it is that we find in the ganglion cells an almost total lack of reproductive capacity; while in many of the gland cells this is slight, in others considerable. In some of the less highly differentiated cells of the body, on the other hand, as in certain forms of epithelium, in blood-cells, and in the cells of the connective tissues, this primitive capacity of protoplasm to form new similar cells by division is maintained, and may be evoked by the changed conditions which injury or loss involves.

Although the occurrence of mitosis is the mark by which we especially recognize the regenerative process in cells, it should be remembered that mitosis or some of its phases may occur in cells, without being followed by those further changes which lead to new cells or new tissues.[1]

We may also often recognize new-formed cells and tissues by differences in the shape and character of the cells and the arrangement of the tissue elements, these often approaching the embryonic type in form as well as in character of development. Furthermore, the atypical arrangement often seen in new-formed cells, both in regard to each other and in their association with older tissues, may aid in the identification of the formative process.

Individual cells, even after having undergone marked structural changes—as, for example, in albuminous degeneration—or after a certain degree of physical injury, may be restored to a normal condition.

After destructive injury or loss, a full and complete replacement of cells and tissues can occur only as the result of a proliferation of cells of the same type as those to be restored. Thus a regeneration of epithelium occurs by proliferation and growth of epithelial cells alone; regeneration of muscle by muscle cells, etc. In fact, however, in the higher types of tissue, after considerable injuries with loss of substance or after destructive pathological processes, complete regeneration is not common. This, as we have seen, is because the highly specialized cells of the body are limited in their capacity for reproduction closely to the domain of physiological regeneration. What we ordinarily call healing in exten-

[1] One is often disappointed in seeking for mitotic figures to find so few of them even in rapidly growing tissues. This is due to the fact that cell division even when active is not continuous, and periods of rest may follow the act of division. See *Thoma*, Text-book of General Pathology, English trans., vol. i, p. 481. For a summary of experimental work on this point see *Woglom*, Study of Experimental Cancer, New York, 1913 (bibl.).

sive wounds of the more highly specialized tissues is usually a provisional makeshift repair by means of new-formed connective tissue.

We have seen that the regenerative capacity in the cells of the human body is most marked in the less highly differentiated types of cells, and that it is above all connective tissues, blood-vessels, and epithelium which most freely and most completely undergo regeneration. These are relatively lowly organized tissues and serve for the maintenance or protection of more highly specialized tissues, and with them regeneration may be complete with full restoration of function.[1] But although the more highly organized tissues in man do not undergo after injury any considerable regeneration, they are, when uninjured, capable, under the stimulus of increased functional exercise, of compensatory hypertrophy, so that the loss to the organism of similar tissue is made good, an example of which is the structural hypertrophy and increased performance of one kidney after the removal of the other.[2]

The capacity to regenerate lost or injured parts exists to a certain extent in all animals but is most marked among the lower forms. Thus if an ameba be cut in two so as to leave one part with the intact nucleus, this part lives and the one-cell organism is completely restored. The fresh-water hydra, composed of many cells, may reproduce a large portion of the organism from a small severed fragment. The common earth worm can reproduce a severed head or tail. Crabs reproduce a whole leg if the severance takes place at a particular joint. Salamanders, snails, etc., can reproduce a leg or foot. It is further noteworthy in this connection that the larvæ of many lower forms, such as reptiles and insects, have a much greater capacity for the reproduction of lost parts than the same species have when in the adult condition.[3]

REGENERATION OF SPECIAL TISSUES.

Regeneration of the Nerve Tissue.—In the nervous system we find no evidence that the ganglion cells are capable of reproduction. Some phases of mitosis are occasionally found in them, although they do not appear to lead to proliferation. But if the essential parts of the ganglion cells, including the nuclei, be intact, a restoration may occur of their central as well as their peripheral branches. The fibrous and the neuroglia tissue of the central nervous system, on the other hand, may increase, and in this way, even with considerable loss of substance, injuries to the brain and cord may undergo a sort of patchwork repair.

In the peripheral nerves extensive regeneration of fibers may take place after injury, when the corresponding ganglion cells are intact. This restoration may be effected in part by fibrous tissue which bridges

[1] Consult *Morgan, T. H.*, Regeneration, New York, 1901; *Barfurth*, Regeneration u. Transplantation in der Med., Jena, 1910; *Korschelt*, Regeneration u. Transplantation, Jena, 1907.

[2] For an illuminating discourse on the surplus of functional provision in the body see *Meltzer*, The Factors of Safety in Animal Structure and Animal Economy, Harvey Lecture, Jour. Am. Med. Assn., 1907, xlviii, 655.

[3] For a suggestive study of the laws of growth and changes in cells and tissues during development and their relationship to the nature and cause of old age, see *Minot*, Harvey Lectures, 1905–1906, p. 230; also Pop. Sci. Monthly, 1907, lxxi, 97.

the damaged region and affords guides or channels along which the axis-cylinders may grow out from the uninjured central segments, finding their way to their endings, as in embryonic development they stretch into the tissues far from the ganglion cells in which they originate. The restitution is possible here because the center of nutrition and at least a limited reparative control in the ganglion cell are intact.

Further details as to degenerations and regenerations of nerves and nerve tracts may be found in the chapter devoted to The Nervous System.

Regeneration of Muscle Tissue.—Regeneration of *smooth-muscle tissue* after injury is slight. Mitosis may occur in the cells, and preliminary phases of division of the body have been described, but it is doubtful whether, except possibly to a very slight extent, new cells are formed. Such healing as occurs after wounds and other injuries is largely effected by new-formed fibrous tissue.

A partial regeneration of *striated muscle* occurs after various forms of damage and losses of substance. There may be division by mitosis in the sarcolemma nuclei (Fig. 47) associated with the accumulation near

FIG. 47.—REGENERATION OF STRIATED MUSCLE AFTER INJURY.
The nuclei of the sarcolemma have proliferated and are surrounded by a small amount of non-striated protoplasm.

them of granular protoplasm, which becomes striated, either in situ or as independent cells. At the injured end of the muscle fiber a similar process may occur, so that these damaged fibers may be in part restored. If as the result of the injury some of the nucleated protoplasm escapes from the sarcolemma, a similar development of striated cells and cell masses may occur.

It is especially in certain forms of degeneration of the contractile substance, after typhoid fever for example, in which the nuclei, the sarcolemma, and the general framework of the tissue are uninjured, that regeneration of striated muscle fibers is most complete. After injuries with considerable destruction of the muscle tissue, regeneration is apt to be irregular and incomplete. While there is often much nuclear division and often the formation of large numbers of more or less striated and variously shaped cells, these are apt not to develop into useful muscle fibers and may disappear by degeneration and absorption or by pressure atrophy. Here, as elsewhere in highly organized tissues, such restitution as is possible after considerable injury is achieved by fibrous tissue.

It is interesting to note that such regeneration as does occur in striated muscle is initiated not by the highly differentiated contractile

substance, but by the nuclei and small residual amounts of undifferentiated protoplasm, and that such more or less definitely striated cells as are formed are in many respects similar to certain forms of developing muscle cells in the embryo.[1]

Although mitosis and nuclear division have been seen in the muscle fibers of the heart after injury, there is no evidence that new muscle can be formed. Repair, which is not infrequent, is secured by fibrous tissue.

Regeneration of Epithelium.—Owing to continuous shedding or to functional destruction of epithelium of the skin and mucous membranes and certain of their adnexa, physiological regeneration by mitosis is common.

After injuries, also, regeneration of epithelium in these situations occurs by mitosis and may be extensive and complete. The new epithelium always forms from the old, and, when surface losses are to be made good, extends inward from the edges across the injured area after a suitable substratum has been formed by fibrous tissue and blood-vessels (Fig. 48).

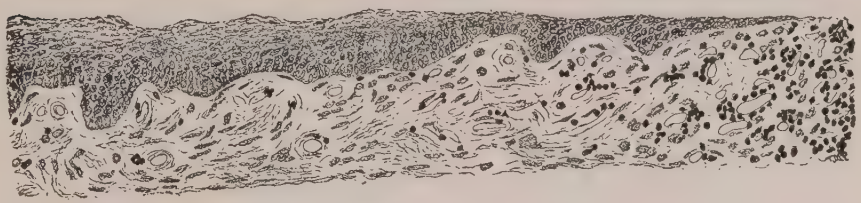


FIG. 48.—REGENERATION OF EPITHELIUM.
From a wound of the tongue. At the left is normal epithelium; at the right the thin pellicle of new-formed cells is extending over the surface of the wound.

The new epithelium is at first atypical in form and arrangement owing to the necessity for a gradual adaptation to the sustaining and associated tissues. Thus the epithelium which at first presses forward over a healing wound of the skin, may be in the form of an irregular layer of cells (see Fig. 49) or of a thin smooth pellicle without the usual variations in size and shape by which it is later characterized when the papillæ of the new cutis are formed and the new cells have adjusted themselves to these and to each other.[2] In stratified epithelium it is the deeper layers from which the new cells chiefly arise. While amitotic division has been observed in the restitution of surface epithelium, this occurs in the more superficial cells and is believed not to be concerned in the regenerative process.

Regeneration of gland epithelium after injury is of frequent occurrence, though this capacity varies considerably in different glands. In many cases it appears to be by a proliferation of the epithelium lining the smaller excretory ducts that the restitution is accomplished, rather

[1] *Pielsticker*, Virchows Arch., 1909, cxcviii, 374 (bibl.); and *Schmincke*, Zieglers Beitr., 1908, xliii, 519; 1909, xlv, 424.

[2] For a study of the regeneration of mucous membranes see *Cornil* and *Carnot*, Arch. de méd. expér., 1899, xi, 413; *Amenomiya, R.*, Virchows Arch., 1910, cci, 231; and *Ascoli*, Arch. p. le sc. méd., 1901, xxv, 257. For repair of bladder mucosa, see *Lasio*, Virchows Arch., 1904, clxxviii, 65.

than by the more highly differentiated secreting cells. This is of especial interest because it affords an excellent example of the rehearsing under abnormal conditions and for reparative ends of a developmental phase of cell life.

In the *liver* very extensive new formation of liver cells may occur after experimental removal of a portion of the organ.[1] These new cells, arising largely from the epithelium of the small gall-ducts, do not form real liver tissue, however, since in this a definite relationship must exist between the liver cells and the gall-ducts, the blood-vessels and the interstitial tissue. Such a relationship can be secured only under the conditions of embryonic development when all the various tissues in-

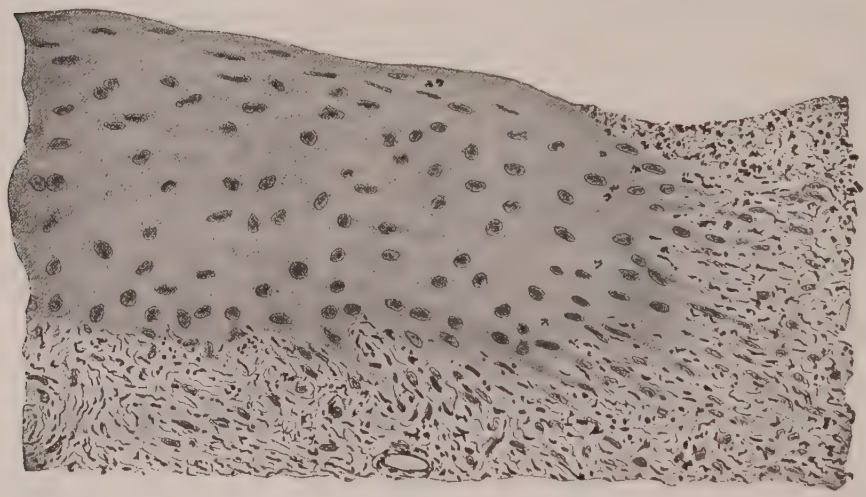


FIG. 49.—REGENERATION OF EPITHELIUM.

The epithelial cells advancing into and over the superficial portion of the granulation tissue at the right are fusiform and irregular in shape. They do not until later assume their usual forms and their relationships to one another and to the underlying tissue.

volved are being formed together. After large destruction of liver cells in certain forms of toxemia—such as acute yellow atrophy of the liver—there may be an extensive and successful regeneration because the associated tissues are not at the same time destroyed.

In the *thyroid gland* new gland tissue may be formed after injury.[2]

In the *kidney* the regenerative capacity of the epithelium appears to be less marked, though proliferation of the epithelium of the collecting tubes may take place and epithelium to a considerable extent may be renewed if the blood-vessels and interstitial tissue remain intact.[3] After poisoning with corrosive sublimate very complete regeneration of epithelium may take place.

Regeneration of epithelium to a considerable extent may take place in the *mammary*[4] and *salivary glands*. But here it is the less highly dif-

[1] *Hess, O.*, Zieglers Beitr., 1913, lvi, 22.
[2] *Halsted, W. S.*, Am. Jour. Med. Sc., 1914, cxlvii, 56; and *Hunnicutt, J. A.*, ibid., 1914, cxlviii, 207.
[3] Consult *Pearce*, Jour. Med. Research, 1909, N. S. xv, 53.
[4] *Ribbert*, Arch. f. mikros. Anat., 1891, xxxvii, 139.

ferentiated cells of the excretory ducts rather than the secreting epithelium through which regeneration is secured. In the *ovary*[1] and *testicle* a slight amount of regenerative capacity may be manifested through mitosis and division of epithelium, but its results are insignificant. The *pancreas* and *spleen* show little or no capacity for regeneration.[2]

In all these cases of partial regeneration it is often difficult to determine how much of the increase in parenchyma, which undoubtedly does occur, is due to a formation of new gland tissue and how much to a compensatory hypertrophy of the old. While, therefore, it is true that after injuries to the glands a considerable regeneration of epithelium may occur, when the loss of substance is extensive it is usually rather by a fibrous-tissue repair or by a compensatory hypertrophy or hyperplasia in the uninjured portions of the organ than by the new formation of true gland tissue that restitution takes place.

Regeneration of Connective Tissue.—We have seen again and again in reviewing pathological regeneration that, in local restoration after injury, fibrous tissue plays an important part, either by itself or in association with various forms of parenchyma. New fibrous tissue readily forms in the adult to replace tissue which has been destroyed. It results from many kinds of prolonged chemical and mechanical irritants. Atrophy of the parenchyma may be followed by interstitial fibrous-tissue growth, or new fibrous tissue may develop under the influence of bacterial and other toxic substances, and it frequently forms dense capsules about the seat of old lesions or around foreign bodies.

Many forms of compensatory fibrous-tissue development will be described in the second section of this book, such as thickening of the walls of blood-vessels, inflammatory adhesions, replacement hyperplasia, etc.

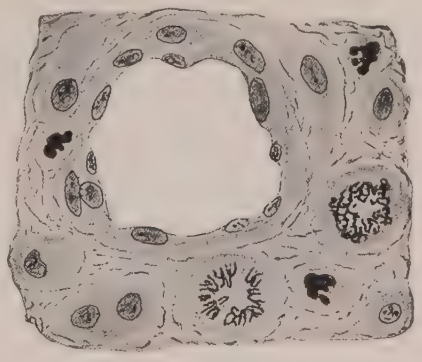


Fig. 50.—Mitosis in Granulation Tissue.

Two of the new-formed connective-tissue cells show mitotic figures. Three leucocytes have wandered into the new tissue.

We have now to consider briefly the changes involved in the new formation of this fibrous tissue. Here, as in all other tissues of the body, it is the cells alone which take the initiative, the formation of intercellular substance being always secondary to the formation of the cells and always occurring under their influence.

New connective-tissue cells may be formed by mitosis (Fig. 50), either from older connective-tissue cells, or, as now seems certain, from the endothelium of the blood-vessels[3] and possibly from the cells of

[1] *Maximow, A.*, Virchows Arch., 1900, clx, 95.

[2] For a study of compensatory hypertrophy of hemolymph-nodes after removal of spleen, see *Weidenreich*, Arch. f. mikros. Anat., 1905, lxvi, 270 (bibl.).

[3] See *Baumgarten*, Arbeiten Path. Inst. Tübingen, 1904, iv, 310.

the adventitia.[1] In either case the cell about to divide shows an increase in the size of the body, which becomes more granular; the nucleus divides by mitosis, segmentation of the cytoplasm following. This process may be repeated so that many cells are derived from one, separated at first by a small amount of homogeneous intercellular substance. These cells,

Fig. 51.—Plasma Cells, Highly Magnified.

at first more or less spheroidal in form, may become larger, and polyhedral or elongated. Little by little, fine fibrils appear between the cells, sometimes apparently as extensions of their cytoplasm, sometimes along their sides in the homogeneous material in which they lie. Such new connective-tissue cells concerned in the formation of fibrillar stroma are called *fibroblasts* (Fig. 52). As the fibrous stroma increases in amount

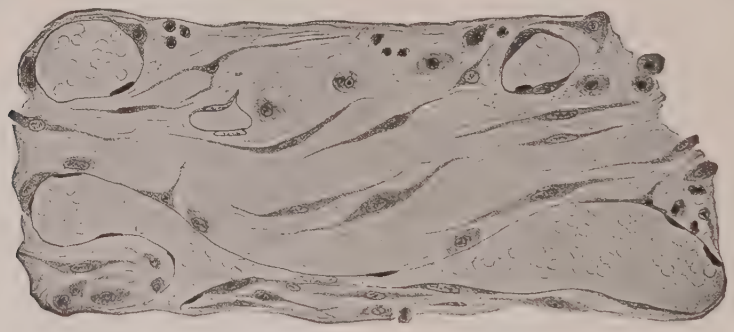


Fig. 52.—Regeneration of Connective Tissue.
Showing fibroblasts with a few new-formed intercellular fibrils between them. The walls of the blood-vessels are very thin.

the cells, at first relatively abundant, become elongated and flattened, until as the new tissue approaches maturity the more or less dense

[1] Plasma Cells.—It has been held that plasma cells are concerned in the formation of new fibrous tissue, but this view has recently been abandoned, and they are now generally believed to be either an independent form of free connective-tissue cell or a modified lymphocyte, this modification appearing only under certain conditions and stimuli. Plasma cells are round or oval cells (Fig. 51), usually larger than the blood or tissue lymphocyte, with an excentric oval nucleus or sometimes two nuclei. The protoplasm contains a fine basophile granulation, and adjacent to the nucleus there is a clear area which contains a central corpuscle. Such cells occur normally in the bone marrow, spleen, lymph-nodes, and gastro-intestinal mucosa, and are found under various pathological conditions, especially in chronic inflammation about the cells of neoplasms and in granulation tissue. Their origin and significance are, however, as yet under discussion, and the reader is referred to larger monographs for details; for example, *Williams*, Amer. Jour. Med. Sc., 1900, cxix, 702; *Schaffer*, Die Plasmazellen; Sammlung anatom. u. physiol. Vortr. u. Aufsätze, Heft 8, 1910; *Weidenreich*, Blutkörperchen u. Wanderzellen ibid., Heft 15, 1911; Die Leucozyten u. verwandte Zellformen, Wiesbaden, 1911.

fibrillar stroma preponderates, pressing the cells between its bundles or layers into variously shaped plaques, often fusiform or linear in profile.

In the formation of fibrillar connective tissue from endothelium the endothelial cells of thin-walled blood-vessels increase in size, and stretch slender bud-like extensions into the adjacent tissue, where, after mitotic division, they assume a rôle altogether identical with that of the ordinary connective-tissue cell. Such cells form a portion of those included under the generic name of *polyblast.*[1] The theory, recently advanced, that connective tissue is formed from fibrin, has not withstood criticism.[2]

The formation of new connective-tissue cells may be large or it may be limited to the production of a single pair of cells; the stroma may be scanty or abundant, loose or dense; the process is essentially the same, namely, the division of cells by mitosis, and the formation by them, or under their influence, of more or less fibrillar stroma. This process, it will be seen, is practically identical with the formation of fibrous tissue in the embryo.

But here, as elsewhere, the character and extent of new tissue production are largely influenced by the environment, and particularly by the nutritive supply, so that the formation of new connective tissue in any considerable amount is closely linked to the development of blood-vessels.

Regeneration of Endothelium.—The regeneration of *endothelium,*[3] which seems to be closely related to that of connective tissue, takes place readily. The new cells advance over denuded surfaces in a manner similar to that in epithelial repair. Whether the new cells always originate in the old neighboring endothelium or are more directly derived from fibroblasts is not yet fully determined.

The Formation of Blood-Vessels.—The formation of blood-vessels in post-embryonic life is believed always to start in a budding or sprouting of the endothelial cells of pre-existing capillaries. The sprouts, directed outward from the endothelia of the capillaries, consist at first of buds, then of slender, conical, or filiform projections of cytoplasmic substance (Fig. 53). Now the cytoplasm of the cell from which the sprout springs may increase in amount and its nuclei divide by mitosis, so that the base of the sprout may consist of a multinuclear mass of cytoplasm or of a cluster of new-formed cells. The sprouts may extend for a long distance into the surrounding region, whether this be already organized tissue in which the vessels are increasing in number or unorganized lifeless material like blood-clot, which is to be replaced by new living structures. If a similar process be in progress in neighboring vessels, the sprouts may unite at their extremities, forming a slender solid protoplasmic bridge

[1] The word *polyblast* is a term introduced by Maximow (Zieglers Beitr., 1902, Suppl.-Heft 5; 1904, xxxv, 93; and Arch. f. mikros. Anat., 1906, lxvii, 680) to designate the cells found in the connective tissues in inflammatory processes. Originally, the term included the small lymphocytes, the plasma cells, the adventitia cells, the clasmatocytes, and the free endothelial cells (the endothelial leucocytes of Mallory) which exist in the tissues in inflammatory processes. Later, Maximow excluded the plasma cells from this group, and other observers have preferred to exclude the lymphocytes also. Marchand's *leucocytoid* cell is synonymous with polyblast (Process der Wundheilung, Stuttgart, 1901).

[2] *Baitsell, G. A.*, Jour. Exper. Med., 1916, xxiii, 739; *Lambert, R. A.*, Proc. Soc. Exper. Biol. and Med., 1916, xiv, 5.

[3] *Oppel*, Virchows Arch., 1901, clxv, 1.

from vessel to vessel. The sprouts now become thickened and gradually channelled out at the base by pressure of the blood in the vessel from which they spring. The blood enters these lengthening channels, forcing its way along them, forming a lumen as it goes. Simultaneously with this advance of the lumen, new nuclei are formed by division of the old along the sides of the vessel, and the new structure gradually assumes a distinctly cellular and vascular character. At length the channel is complete; the new vessels have well-defined endothelial walls and connective-tissue cells from without, or new connective-tissue cells which have been formed about the nuclei of the protoplasmic sprout, range themselves outside along the walls. So the new vessel takes its

Fig. 53.—Developing Blood-vessels in New-formed Tissue.

place in the vascular system of the part. Thus, in a short time, many new blood-vessels may form, furnishing nutritive centers about which the organization of tissue proceeds.[1]

In the new formation of arteries it is believed that the smooth-muscle tissue is formed by a growth along the developing vessel from a pre-existing artery.

The Formation of Lymph-Vessels.—The formation of lymph-channels in granulation tissue takes place in the same way as that of blood-vessels, the process being initiated by the formation of buds from the endothelium of existing vessels which push their way out into the new tissue, gradually acquiring lumina and forming anastomoses with other trunks.[2]

Regeneration of Cartilage and Bone.—New *cartilage* may form by the proliferation either of connective-tissue cells or, to a slight extent, of cartilage cells, and the formation about the new cells of the characteristic basement substance. It is the connective-tissue cells of the perichondrium especially from which new cartilage is formed.

The new formation of *bone* under pathological conditions is not brought about by the bone cells, but by the development, first, from the cells of the periosteum or of the marrow, of a cellular connective tissue,

[1] *Faykiss*, Beitr. klin. Chir. (Bruns), 1908, lviii, 606.
[2] *Talke, L.*, Zieglers Beitr., 1902, xxxii, 106.

or from the perichondrium of a form of hyaline cartilage.[1] From these tissues, by processes essentially similar to those in the embryonic development, the new bone is formed under the influence of osteoblasts (page 1062).

The regeneration of *bone-marrow* takes place through the activities of the characteristic marrow cells together with those of the blood-vessels and cells of the connective tissue and osteoblastic type.[2]

Regeneration of Lymph-Nodes.—Regeneration of lymph-nodes may take place after partial removal. This appears to be more complete in the earlier years of life. After extirpation of lymph-nodes it has been shown experimentally that new nodes may form. These Bayer[3] believed develop from fat tissue. Further studies are needed in the regeneration of lymph-nodes and the relationship of these and lymphatic tissue to fat and other forms of connective tissue.[4]

Regeneration of Fat Tissue.—Fat tissue is formed by the accumulation of fat droplets in the cells of various types of connective tissue, particularly in the young or embryonic forms; but adult connective tissue

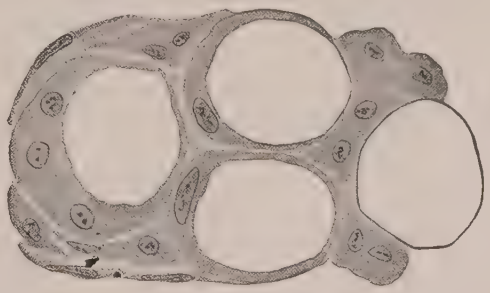


FIG. 54.—REGENERATION OF FAT TISSUE.
The new-formed fat cells show a rim of cytoplasm containing the nucleus, which has been crowded to the sides of the cells by the accumulating fat.

may change into fat tissue by a similar process. The repair of fat tissue takes place by the formation of young fibrous tissue, whose cells and stroma gradually assume the type of fat tissue. The cells of regenerating fat tissue are at first more or less spheroidal, and remnants of the cytoplasm may be seen as more or less crescentic masses pressed to one side by the accumulating fat (Fig. 54). New fat tissue which replaces atrophied organs or parts of organs, such as kidney, heart, lymph-nodes, etc., is formed in the same way.[5]

Regeneration of Blood.—The formation of leucocytes appears to occur chiefly in the masses of lymphoid and myeloid tissue which are so widely scattered throughout the body in the lymph-nodes, the spleen, and the bone-marrow. In adult life the lymphocytes are probably formed

[1] *Wolff, J.*, Virchows Arch., 1885, ci, 572; *Fujinami, A.*, Zieglers Beitr., 1901, xxix, 432.

[2] For studies on the regeneration of bone-marrow, see *Haasler*, Arch. f. klin. Chir. (Langenbeck), 1895, l, 75; and *Enderlen*, Deutsch. Ztschr. f. Chir., 1899, lii, 293.

[3] *Bayer*, Arch. f. klin. Chir. (Langenbeck), 1895, xlix, 637.

[4] Consult for bibl. of regeneration of lymph-nodes and lymph-vessels, *Meyer*, Bull. Johns Hopkins Hosp., 1906, xvii, 185; also, *Hammerschlag*, Virchows Arch., 1908, cxciv, 320.

[5] For a study of regeneration. inflammation, etc., in fat tissue see *Kraus*, Ztschr. f. Heilk., 1906, xxvii, 243.

wholly in the lymph-nodes, and the granular leucocytes in the bone-marrow; in anemia and leukemia, however, new areas of myeloid and lymphoid tissue rapidly appear, and these assist the hyperplastic nodes and marrow in the production of large numbers of red and white cells. Under these conditions, a considerable proportion of the cells produced are distinctly abnormal in type and imperfect in structure. These lymphoid and myeloid areas are most frequent in the nodes, spleen, liver, and kidney.[1] Regeneration of *red blood-cells* seems to occur in the bone-marrow and possibly in the spleen and hemolymph-nodes through mitotic division of nucleated forms. The latter may, under pathological conditions, appear in the vessels in varying numbers (see Part II, Chapter I).[2]

TRANSPLANTATION OF TISSUE.

Transplantation of various types of tissue has been frequently attempted, and is, on both theoretical and practical grounds, of considerable interest. Transplantations have been successfully made from one part of the individual to another—*autoplastic*—or from another individual of the same species—*homoplastic;* but not from one species to another.

A variety of general conditions favor successful transfer. The tissue to be transplanted must be alive and in good condition; young tissues are more readily transferred than old; the site to which the transfer is made must be adapted to the growth of the graft. A great difference is observed in the success of transplantation of various types of tissue. Thus, the epithelium of the skin and various forms of connective tissue may be, under favorable conditions, readily transplanted, and produce new tissue of similar type. Thus, deeply implanted epidermal tissue may grow and produce considerable new tissue, especially in the form of cysts resembling either simple or complex dermoid cysts. Experimental transplantation to another individual of the same species, of various gland and other special forms of tissue, such as portions of the kidney, liver, sebaceous, salivary and mammary glands, testicles, ovary, periosteum, bone, and cartilage, shows that there may be at first, if the conditions be favorable, a slight proliferation of the transplanted tissue cells. Together with this growth in the better-nourished parts of the tissue grafts there is apt to be a more or less extensive necrosis of other portions. But the proliferative activities of transplanted gland tissue are, as a rule, not permanent; they presently cease and sooner or later these tissues, with necrotic portions of the grafts, are absorbed.

The body seems to react sooner or later to a transplanted organ as to a foreign body, and to accomplish its destruction in much the same fashion as in the case of invasion by infective agents.

The many reported instances of successful homoplastic organ trans-

[1] *Sternberg*, Zieglers Beitr., 1909, xlvi, 586; *Werzberg*, Virchows Arch., 1911, cciv, 272; *Askanazy*, Virchows Arch., 1911, ccv, 346; *v. Domarus*, Arch. f. exper. Path. u. Pharmakol., 1908, lviii, 319.

[2] For a general and extended study upon tissue regeneration see *Marchand*, Process der Wundheilung, Stuttgart, 1901.

plantation lack a sufficiently careful anatomical control of the organs so transplanted. It is undoubtedly possible to make homoplastic transplantations of the thyroid,[1] the parathyroid, the thymus,[2] the spleen,[3] and the ovary; but after a shorter or longer period such transplanted tissue usually undergoes atrophy. If very large series of animals are used, a few successes will usually be obtained, often not more than one or two per hundred. Such homoplastic grafts succeed, therefore, in about the same proportion as transplants from primary tumors. Marine has found that thyroid grafts may remain alive for a long period.

Transplantation of epidermis for practical purposes has become a part of surgery, aiding in the repair of surface losses of skin. The graft properly implanted upon the granulating surface becomes closely attached by the growth into it of new connective-tissue cells and blood-vessels. The old connective tissue of the graft, as well as most of the epithelium, especially the superficial layers, usually dies and is cast off or absorbed, while new epithelium formed from the remaining cells makes its way over the granulating surfaces.

In transplantations of bone the grafts seem to furnish a nidus into which, hand-in-hand with its absorption, new bone grows under the influence of osteoblasts of the old periosteum, but does not itself apparently share in the new production of bone tissue. The transplantation of periosteum is possible, and new bone will form from it.[4]

The possibility of successful autoplastic transplantation of organs has been shown by Carrel and others.[5] In individual cases the results have been excellent, but the total number of successes is small and the surgical difficulties are enormous; and as the procedure has but little practical value it may be regarded simply as a demonstration of the possibilities of laboratory surgery.

The only important practical form of transplantation is the homoplastic or heteroplastic, and certain recent investigations point toward the possibility of its ultimate accomplishment. Bashford[6] and Da Fano[7] some years ago showed that the resistance to tumor transplantation was not humoral, but was a factor of tissue activity and apparently correlated with the lymphocytic and plasma cell reaction in the neighborhood of the cells of the neoplasm. Working along this line, Murphy[8] has found that the growth of tissues in vitro is inhibited by the presence of growing bone-marrow or spleen. After interference with the activity of these organs by treatment of the animals with Roentgen rays, which are known

[1] For study of transplantation of thyroid see *Payr*, Arch. f. klin. Chir. (Langenbeck), 1906, lxxv, 730; *Manley, O. T.*, and *Marine, D.*, Jour. Am. Med. Assn., 1916, lxvii, 260.

[2] *Marine, D.*, and *Manley, O. T.*, Jour. Lab. and Clin. Med., 1917, iii, 48.

[3] *Manley, O. T.*, and *Marine, D.*, Jour. Exper. Med., 1917, xxv, 619; 1920, xxxii, 91.

[4] *Bancroft, F. W.*, Am. Jour. Med. Sc., 1914, cxlvii, 809 (bibl.).

[5] *Carrel*, Trans. Internat. Cong. of Surg., 1914. *Payr*, Arch. f. klin. Chir. (Langenbeck), 1900, lxii, 47; Verhandl. d. deutsch. Gesellsch. f. Chir., 1908, xxxvii, 105; *Dederer*, Jour. Am. Med. Assn., 1918, lxx, 6. For an extremely thorough and conservative study of transplantation, with bibliography, see *Schöne*, Die heteroplastische u. homöoplastische Transplantation, Berlin, 1912.

[6] *Bashford, E. F., Murray, J. A.*, and *Haaland, M.*, Ztschr. f. Immunitätsforsch., Orig., 1909, i, 449.

[7] *Da Fano, C.*, Ztschr. f. Immunitätsforsch., Orig., 1910, v, 1.

[8] *Murphy, J. B.*, Jour. Exper. Med., 1913, xvii, 482; 1914, xix, 513; Jour. Am. Med. Assn., 1914 lxii, 1459; *Murphy, J. B.*, and *Morton, J. J.*, Proc. Nat. Acad. Sc., 1915, i, 435; Jour. Exper. Med. 1915, xxii, 204.

to be especially destructive to lymphoid and marrow tissue, it was found that grafts of a mouse sarcoma would grow in irradiated rats for a longer time than in controls. Should the results of this experiment be shown to be more generally true, they may point the way to the possibility of successful heteroplastic surgery; but as yet confirmation is lacking, and those who have recently investigated the subject are unable to confirm Murphy's findings.[1]

The Impulse to Cell Regeneration.

While we can thus summarize the differing capacities of the body-cells for regeneration; while we know many of the general conditions under which the impulse to cell proliferation and growth is manifested; while, further, we have learned something of the delicate mechanism through which division is controlled and effected, at the end we must acknowledge that we do not know why cells divide. We may say that it is due to a chemical or a mechanical stimulus, and it certainly may be associated with both; or that increased nutrition favors, while innutrition retards cell multiplication; we may cite direct or remote injury, or talk of the inhibition of organic control, disturbed tissue equilibrium, diminished pressure, reversion, etc., but when all is said we are forced to recur to some unknown factor in the inherited constitution of the cell which determines the measure and character of its response to the most varied influences.

The hypothesis of Ribbert, in accordance with which the capacities of cells to proliferate and grow, so manifest in embryonic life, are held in restraint in the normal adult body by a subtle correlation of cells and tissue, is most suggestive in this connection. When this mutual relationship is disturbed, as is the case under many of the conditions in which regeneration takes place, the cells, in the conception of Ribbert, are freed from certain, at least, of their organic restraints. These restraining conditions he calls "tissue tension," meaning thereby, however, something more complex and subtle than simple physical tension. Thus, free to exert their primitive capacities, formerly held in restraint by the environment, we can conceive how cells proliferate and new tissues are formed in the regenerative processes without assuming the acquirement of any new capacities and without the assumption of vague and special stimuli.[2]

According to this conception, then, the regenerative processes leading to the formation of new cells and tissues are not brought into play by stimuli furnished by injuries—the so-called "formative stimuli" of an

[1] *Sittenfield, M. J.*, Jour. Cancer Research, 1917, ii, 151; *Stevenson, H. N.*, ibid., 1918, iii, 63.

[2] For a résumé of Ribbert's hypothesis and its applications to regeneration, hypertrophy, etc., see *Ribbert, H.*, Allgemeine Pathologie, 5th edition, Leipzig, 1915. For a criticism of these views, see *Adami, J. G.*, Principles of Pathology, Philadelphia, 1908, vol. i, p. 537 et seq.

See also, for summary of a new phase of research and interpretation in the nature of the "formative stimulus" involved in artificially induced cell division and artificial parthogenesis, *Loeb, J.*, Studies in General Physiology, Chicago, 1905, p. 253; Artificial Parthenogenesis and Fertilization, Chicago, 1913; and also, Science, 1915, xli, 704. For general bibliography of regeneration, compensatory hypertrophy, etc., see *Aschoff, L.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 22. For a full consideration of the subjects dealt with in this chapter, consult *Chantemesse* and *Podwyssotsky*, Les Processus généraux. I, Paris, 1901.

earlier time. But new cells and tissues form as the result of the release of inherent capacities of cells normally held in restraint after the developmental period, by their associations as parts of an organism. Thus, when conditions of nutrition, pressure, organic association, possibly of protoplasmic continuity or of nerve correlation, are disturbed, for example, through trauma, poisons, degenerations, prolonged hyperemia and various other vascular and nutritive cellular disturbances, the leash of organic control is loosened, and the primitive capacities of the cells are temporarily free to act. As we have seen, however, this resumption of an abeyant potency in the ordinary processes of repair is not limitless and, sooner or later, the old controlling relationships of organic associations are re-established and the reparative activities cease.[1]

It is important, however, to dissociate the capacity to stimulate the growth of organs or even of whole organisms from the power to incite similar increased growth rates in cells. The addition of thyroid, pineal, or thymus gland tissue[2] to the water in which tadpoles are living seems to increase the growth rate, but neither of these substances stimulates growth in tissue cultures when the cells are separated from the influences of the nerves and the supply of foodstuffs through the blood or lymph. It is now well established that the pineal and pituitary glands control sexual development and growth of the body as a whole;[3] but the glandular substances or their extracts fail to influence either tissue cultures or tumor implants.

The example most often cited as an evidence of direct growth stimulus is the extensive epithelial proliferation induced by the injection of dyes, such as Sudan III or Scharlach R, oils, tars, and many similar materials, into the corium. But it has been shown by very extensive experiments[4] that all these substances act in the familiar way by causing necrosis with consequent regeneration of the injured tissue and an excessive production, if the irritation is long continued. If such irritation is kept up for a sufficient length of time in animals of cancer age, epitheliomata may develop.[5]

Again, it has been shown that there can be extracted from the corpus luteum and the placenta, substances of uncertain chemical nature which have an extraordinary power of inciting growth of the uterus and mammary gland. These hormone-like substances are capable also of stimulating subcutaneous grafts of uterine musculature and apparently of prolonging the life of such grafts.[6] A similar stimulating effect has been observed when thyroid grafts are treated with iodine;[7] but such stimulation is not noted in tissue cultures. Nevertheless, it is possible by suitable threshold exposures of such tissue cultures to *x*-ray or radium,[8]

[1] For a consideration of the bearing of this hypothesis on compensatory hypertrophy, see *Ribbert, H.*, Lehrbuch d. allg. Path.,. 5th edition, Leipzig, 1915.

[2] *McCord, C. P.*, Surg., Gynec., and Obst., 1917, xxv, 250 (bibl.).

[3] *Cushing, H.*, The Pituitary Body and Its Disorders, Philadelphia, 1912.

[4] *Bullock* and *Rohdenburg*, Jour. Med. Research, 1915–16, N. S. xxviii, 53.

[5] *Yamagiwa, K.*, and *Ichikawa, K.*, Jour. Cancer Research, 1918, iii, 1. For the experimental production of sarcoma of the liver of rats, see *Bullock, F. D.*, and *Curtis, M. R.*, Proc. N. Y. Path. Soc., 1920, xx, 149.

[6] *Frank, R. T.*, Surg., Gynec., and Obst., 1917, xxv, 329.

[7] *Manley, O. T.*, and *Marine, D.*, Jour. Am. Med. Assn., 1916, lxvii, 260.

[8] *Prime, F.*, Proc. New York Path. Soc., 1916, xvi, 90.

or by similarly exposing eggs of the lower animals, to obtain distinct increase in growth rapidity, so that it is not possible to deny that a direct growth stimulus may exist. It is, however, evident that the question has not yet approached solution.

With protozoa, such as paramecium, which can be isolated and controlled in pure culture for long periods, many interesting phenomena have been observed. Rhythmic alterations of rapid and slow division have been traced, a phenomenon seen also in transplanted tumors. Regeneration of the strain after conjugation had been thought necessary for the continuance of the race,[1] but Woodruff[2] has demonstrated that if sufficient nutriment is supplied, the strain may be carried for at least five thousand generations without conjugation.

After the development of the technique of tissue culture as initiated by Loeb and furthered by Harrison, Carrel, Lambert, and others,[3] and the discovery by Murphy that tissues, and especially tumors, will grow in the membranes of the chick embryo, it was hoped that this addition to our experimental machinery would solve many questions concerning the biology of the cell. But, unfortunately, many limitations have been found which render the method less useful than it was thought. For while the simpler embryonic tissues may be cultivated for many generations, adult tissues, complex organs, and especially tumors, grow with difficulty or not at all. The limit of time is measured in days, rather than, as was originally thought, in months, and the positive chemotaxis of the fibrin of the clot in which the tissue particles are placed, seems necessary for the induction of any considerable outgrowth. Little or no growth is obtainable in serum, even if support is given the cells by artificial networks of bolting-cloth or perforated collodion membranes. Even in the embryo chick membranes, the growth of tissues, while at first vigorous, rapidly diminishes, and after a few weeks a tumor has to be "refreshed" by several passages through a suitable animal.[4]

The conditions which underlie the extraordinary emancipation from tissue restraints exhibited by the growth of the cells of malignant tumors are still entirely unknown.

The study of the vital activities of cells has been facilitated by the ingenious apparatus devised by Tashiro, which permits the measurement of the extremely minute quantities of carbon dioxide given off from even a single protozoon.[5]

[1] *Calkins, G. N.*, Arch. f. Entwickelungsmechanik d. Organismen, 1903, xv, 139.

[2] *Woodruff*, Arch. f. Protistenkunde, 1911, xxi, 263; Jour. Exper. Zool., 1911, x, 557; ibid., 1913, xiv, 575.

[3] For a résumé of technique and results of cultures of adult and embryonic tissues see *Harrison*, *Lambert*, and *Burrows*, Jour. Am. Med. Assn., 1913, lx, 1660; *Carrel*, Physiological Reviews, 1924, iv, 1 (bibl.); and *Fischer*, Zeit. f. Krebsf., 1927, xxv, 89.

[4] *Stevenson, H. N.*, Proc. New York Path. Soc., 1916, xvi, 60.

[5] *Tashiro, S.*, A Chemical Sign of Life, Chicago, 1917.

CHAPTER V.

INFLAMMATION.

General Considerations.

The conception of inflammation was originally a clinical one in which the process was marked by special symptoms—redness, heat, swelling, pain, and impaired function. This conception was gradually enlarged to embrace the new formation of tissue which might be associated with or follow these symptoms, or which might be independent of them. After the knowledge of the importance of the cell became general it was upon the formation and accumulation of cells and other substances that attention was especially fixed. Finally, the processes and structural alterations embraced in the conception of inflammation became so varied and complex that a definition or even a characterization seemed not only difficult, but wellnigh impossible.

It is only within the past decade or two that the processes and lesions involved in inflammation have been seriously considered in the light of comparative pathology and as biological problems divorced for purposes of research from the dominance of traditional clinical conceptions. In view of our increased knowledge of the structure of cells and of the impulses immediate and hereditary which determine their performances, it seems possible now to resolve the complex processes and lesions embraced in the general notion of inflammation into more simple factors, and to arrive, if not at an exact definition, at least at a reasonable conception of the relationship of its phenomena to each other, to those of normal physiology, and to other phases of disease.

With this end in view it seems wise at first to rehearse as simply and briefly as is practicable some of the more typical of the phenomena and lesions which are commonly grouped under the term inflammation.

While the death of tissue from trauma, and degenerative alterations in the tissues in the presence of various forms of poisons are often important factors in the inflammatory processes, we shall not consider them separately here, because they are incidental rather than inherent and have already been treated in the section on Degenerations and Necrosis. But it should be noted that various phases of albuminous degeneration, local or general, which are induced by the poisons of the pathogenic bacteria, are very often associated with inflammation, and not infrequently modify, or may even determine, its occurrence.

A comprehensive survey of the conditions under which inflammation most frequently takes place shows at once that it is almost always associated with some form of injury. This may be direct trauma, or excessive heat or cold. It may be poisons of various kinds—from the cruder

inorganic poisons inducing immediate and gross tissue destruction to the subtle toxic substances which result from the metabolism of micro-organisms or from the aberrant metabolism or degeneration of the body-cells themselves. Dead cells or tissues or foreign substances of many kinds within the body are common incitants of the inflammatory processes.

Let us now look at some of the ways in which the living body responds to injury, considering first an injury which is very slight and simple.

Types of the Inflammatory Reaction of the Body to Injury.

Injury to Non-vascular Tissue.—If a small clean cut be made in living fibrillar connective tissue, not involving blood-vessels, and affecting only the cells and fibers in the vicinity of the incision, and if the sides of the wound be immediately placed and held together, the resulting changes which lead to the complete restitution of the part are comparatively simple. A small quantity of fluid which oozes from the tissue spaces sticks the sides of the cut together. Such connective-tissue cells as have been seriously injured, especially if the nuclei have suffered, die and disintegrate; and these, together with such tissue fragments as may be present, are removed by phagocytes or through autolysis and absorption. But cells whose nuclei have remained intact, whether directly upon the incision or in its immediate vicinity, become larger and more granular, may divide by mitosis, extend their bodies or processes across the plane of incision, bridging this at intervals with living protoplasm. Under the influence of these cells, new intercellular fibers are formed, which in a short time bind the sides of the wound firmly together (Fig. 55). Thus, with but the slightest amount of tissue destruction, and with no involvement of the blood-vessels, a simple mechanical injury may be made good. This form of reaction to injury of living tissue is known to the surgeons as *healing by "first intention."* The mode of healing does not essentially differ if there be a slight injury to the blood-vessels.

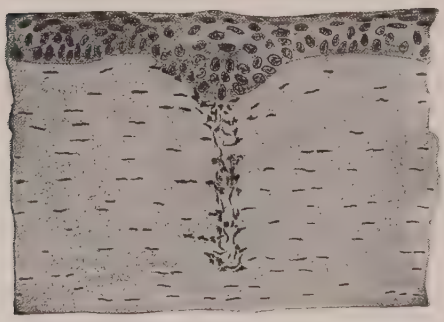


FIG. 55.—HEALING OF A WOUND OF THE CORNEA.

Without involvement of blood-vessels a few new connective-tissue cells have formed along the line of slight injury (incision), and the sides of the wound are joined by the new cells and fibrils formed by them. The epithelium has regenerated over the surface.

In injury to a non-vascular part, like the cornea, for example, the primary reaction to the damage manifested by the fixed connective-tissue cells is often complicated by the wandering in of leucocytes from the conjunctival blood-vessels in the manner indicated in the next section. This participation of distant blood-vessels and leucocytes is, no doubt, incited by a reflex stimulation of the nerves of the blood-vessels and may

be fostered under certain conditions by the absorption of injurious substances which are carried to the nearest blood-vessels by the lymphatics. Thus it is that in injuries to the cornea, a non-vascular part, the lesion is often complicated by the secondary participation of the adjacent blood-vessels.

Injury to Vascular Tissue.—Let us now look at the effect on a vascular tissue of an injury not immediately destructive. For this purpose the mesentery of the bladder of a curarized frog, drawn out upon a suitable plate [1] upon the stage of the microscope and kept moist by irrigation with 0.75 per cent. salt solution, affords a succession of most instructive pictures. The mechanical disturbance of the organs exposed, desiccation, and a variety of other physical and chemical vicissitudes to which they are subjected, are sufficiently damaging to incite a complex train of responses on the part of the living tissues.

In studying the circulation of the blood in small vessels under the microscope it should be remembered that, while the walls of these vessels are made up of living tissue and are capable of responses by movement or by structural change to external agencies, whether applied directly or through the nerves, they are also elastic pipes through which fluid flows, and that both pipes and fluid are subject to the laws of mechanics. These mechanical laws are often modified in expression, it is true, by the subtle energies which living tissues wield, but, as Thoma more than any other has shown, they are not to be ignored by the serious student of the living body, either in health or disease.

In the bladder or mesentery of the frog the arteries and veins with their connecting system of capillaries are clearly seen. When the current is rapid the cells of the blood in the arteries and veins are gathered into a red axial mass in which the separate cells may not be distinguishable, owing to their crowding and the rapid flow. Outside of this, against the walls, is a clear marginal zone in which a leucocyte is occasionally visible. If for any reason the rate of flow be considerably diminished, the leucocytes, which are specifically lighter than the red cells, gather in the marginal zone. If the current become very slow or be arrested, the marginal zone disappears and the red and white cells intermingle.[2]

Soon after the exposure of the bladder or mesentery the tissues become hyperemic.[3] The arteries, veins, and capillaries dilate, and the blood, encountering less resistance from the walls, flows more rapidly through them. This increased rapidity of the blood current does not, however, last long, although the vessel still remains dilated. After a variable period, owing, it is believed, to changes in the endothelia of the vessels, the blood meets with so much resistance that it flows more slowly than under normal conditions. Temporary or even permanent stasis may occur in some of the vessels, but this is not a constant nor a

[1] See description of Thoma's frog-plate, p. 131.

[2] This distribution of the blood is almost, if not wholly, mechanical, and may be simulated in glass tubes with a fluid in which lifeless particles of different specific gravities are suspended. The particles of the lesser specific gravity assume, when the flow is established, the peripheral portion of the stream.

[3] For a review of some of the factors governing vascular dilatation and slowing of the blood stream, see *Woolley*, Jour. Am. Med. Assn., 1914, lxiii, 2279.

characteristic occurrence. White blood-cells—leucocytes—now begin to accumulate along the inner walls of the veins and to become fixed there, so that after a time the whole inner surface of the veins may be more or less thickly sprinkled, and even closely crowded, with adherent leucocytes. These may either lie firmly against the endothelium or be dragged slowly along by the current of blood sweeping past them. Some are dragged by the blood current into pyriform shapes, showing that they are adherent at a small point only, and thus they may be detached from the wall and rejoin the circulating blood. They may by ameboid movement crawl slowly along the interior of the wall, even against the current. In the capillaries, also, a similar comportment of the leucocytes may be seen.

After a time, which varies considerably—in the bladder sometimes within an hour after its exposure; in the mesentery usually later—some of the leucocytes commence to make their way slowly through the walls of the veins and capillaries. At first a little shining knob appears on

FIG. 56.—EMIGRATION OF LEUCOCYTES FROM THE BLOOD-VESSELS OF THE MESENTERY OF THE FROG.
Some of the leucocytes are clinging to the interior of the vessels; some are passing through the walls; some are wandering away through the tissue spaces. There has been diapedesis of a few red blood-cells.

the outside of the wall opposite to the cell which is sticking within, and this outer portion grows larger as the part still within grows smaller, until at length the entire cell is outside of the vessel. The cell now may immediately detach itself and wander off in the tissue spaces, or it may remain for some time attached to the outside of the wall (Fig. 56). This passage of the leucocytes through the walls of the capillaries and veins—it does not occur in the arteries—is called *emigration*. The emigrating cells are largely the polynuclear leucocytes, but mononuclear forms—lymphocytes—and eosinophiles may also pass out of the vessels.

The cells pass between the endothelia through the cement substance, which apparently is in some way changed in the inflammatory process. They may pass through very rapidly, but usually their progress is slow and often interrupted, so that cells may be seen motionless for a long

time in various stages of progress through the walls. A half minute or even less, may suffice for their passage, or they may be hours about it. Thus, after a variable time, if the conditions have been favorable, the tissues immediately around the capillaries and veins, and even those somewhat remote from them, may be more or less densely crowded with leucocytes, some motionless and in the spheroidal form, others moving about through the tissue spaces (Fig. 57). Leucocytes may pass out of the tissues on to free surfaces of the inflamed part, or they may wander into the lymph-vessels and so re-enter the circulation.

It is probable that the emigration of the leucocytes is due in part to a sort of filtration process with which the pressure of the blood within the vessels is concerned, and also to capillary attraction at the point of emergence. But the inherent contractility of the cells themselves forms,

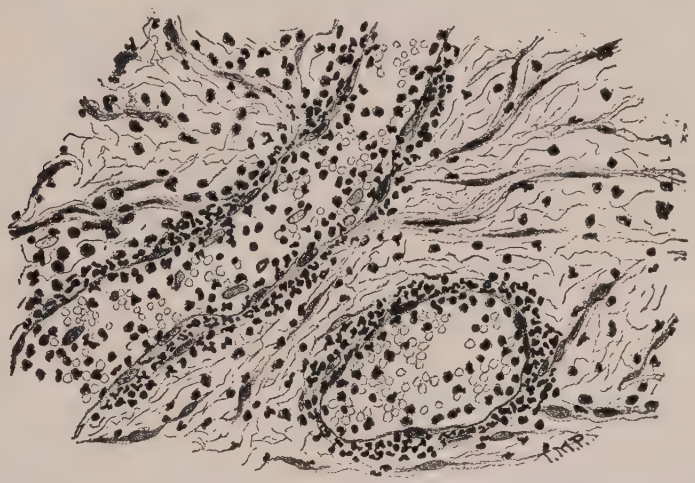


Fig. 57.—Exudative Inflammation in the Wall of the Appendix Vermiformis. Showing extravasated leucocytes in the vicinity of the blood-vessels, with edema of the surrounding connective tissue.

doubtless, a very important factor.[1] That in most cases *chemotaxis* plays a significant part in directing the course of the leucocytes seems to be well established, and it is largely to this agency that the gathering of leucocytes in the vicinity of the deleterious substances which incite inflammation is due.

In regard to chemotaxis it should be said in brief that the direction of locomotion in protoplasm may be determined by chemical substances in the vicinity. This is the case not only in the lower forms of life, as in certain bacteria and protozoa, but also in such cells of higher organisms as have retained a certain independence of locomotion, for example, in the leucocytes and certain cells of the connective tissue. To this form of response to external agencies the name *chemotaxis* has been applied. In

[1] For a discussion of the various factors, see *Schridde*, Studien u. Fragen z. Entzündungslehre, Jena, 1910; *Löhlein*, Gesetze d. Leukozytentätigkeit bei entzünd. Prozesse, Jena, 1913; *Marchand* Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 5.

some cases the effect of chemical agents in the environment is not to attract, but to repel, protoplasm. This has been called *negative chemotaxis*. Chemotaxis and certain allied responses to outside influences have been found to play an important rôle in health as well as in some forms of disease, and have been the subject of much careful study.[1]

If we return now to our observation of the living mesentery it will be found that while emigration of leucocytes is going on, the red blood-cells, although for the most part carried along as usual in the current of the veins and through the capillaries, still often find their way in small, and sometimes in very large, numbers into the surrounding tissues. They are, it is believed, carried passively through the cement substance between the endothelia by minute streams of fluid which under these conditions are flowing in abnormal quantities through the walls. This extravasation of the red blood-cells is called *diapedesis*. It appears to follow the emigration of the leucocytes, which seems in some fashion to prepare the way for the more mechanical exit of the red cells.

By this time it will usually be found that the tissue around the vessels is somewhat swollen and more succulent than normal, and fluid may be poured out on the free surface. The fluid which thus gathers is called *serum*. It is similar to the simple non-inflammatory transudates, except that it is richer in proteins and is mixed with cells. This serum has passed out of the blood-vessels along with the blood-cells, and, as its composition differs somewhat from that of blood-plasma, it is evident that it has undergone a change as it passed. The way in which this alteration in the composition of the blood-plasma occurs as it passes through the walls of the vessels and becomes the serum of exudation, we do not understand. But it is probably due to metabolic processes in the endothelial cells by which what has been called a "selective filtration" is secured.

Fig. 58.—Fibrin in Inflammatory Exudate.

The fluid exudate contains fibrinogenous substance, and from this, when the conditions are favorable, *fibrin* may be formed (Fig. 58) by a change similar to that which occurs in the coagulation of the blood. The leucocytes which wander into the tissue spaces outside the vessels may encounter conditions inimical to life, from innutrition or from the presence of deleterious substances, and thus these and other cells furnish, as they die and disintegrate, the fibrin ferment essential to coagulation. Clusters of fibrin fibrils may thus often be seen surrounding dead and disintegrating cells (Fig. 59).[2]

If at this time the exposed bladder or mesentery of the frog be

[1] For a fuller consideration of chemotaxis, with bibliography, consult *Davenport*, Experimental Morphology, Part I., p. 32 *et seq.*; *Verworn, M.*, Allgemeine Physiologie, 5th edition, Jena, 1909; *Bayliss, W. M.*, Principles of General Physiology, London, 1924. For the forms of leucocytes which emigrate under various conditions see *Adler*, A. Jacobi's Festschrift, 1900, p. 309.

[2] For a discussion of the relationship of fibrin formation to cells which may furnish a substance inducing coagulation see *Hauser*, Virchows Arch., 1898, cliv, 335; also *Arnold*, Centralbl. f. allg. Path., 1899, x, 313.

restored to the abdominal cavity and the animal placed under favorable conditions, the reaction of the vessels and cells to the unusual environment may, if the injury have not been too severe, gradually subside. The circulation is then re-established, the serum is absorbed, the leucocytes which have not come out upon the surface or died in the tissue spaces may re-enter the lymphatics. Fibrin, if this have been formed, and red blood-cells which have escaped from the circulation are disposed of under the influence of ferments which leucocytes furnish (page 125), or may be carried off by the wandering leucocytes; or, as is not infrequently the case, blood pigment resulting from the reduction of the hemoglobin which leaves the red blood-cells by osmosis may remain for some time, in situ, as the only mark of an earlier active inflammatory process.

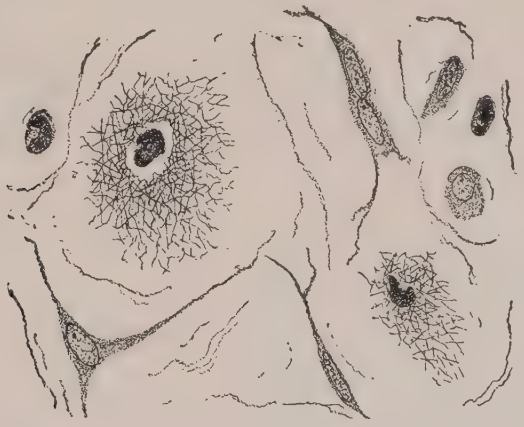


Fig. 59.—Fibrin Forming Around Dead Cells in the Interstices of Tissue.

Thus in the living animal[1] we can learn by direct observation the way in which the serum, fibrin, and red and white blood-cells get into tissues and upon free surfaces in certain forms of injury involving the blood-vessels.

We can see also by this experimental observation just what the factors are which induce the so-called "cardinal symptoms" of inflammation—the redness and heat due to hyperemia; the swelling to accumulation of exudate; the pain to pressure on the nerves; and the impaired function to the disturbances of nutrition to which all of these factors contribute. The materials gathering in or upon the tissues under these conditions are called *exudates*, and this phase of inflammation is commonly called *exudative inflammation.*

Hand-in-hand with these changes, which are directly associated with lesions of the blood-vessels, there occur alterations of the cells of the affected part, especially of the connective-tissue cells, which are not readily observed in the experimental animal. These may suffer regressive changes—albuminous or fatty degeneration or necrosis; or, on the

[1] Thoma has shown by similar studies on warm-blooded animals that the reaction to injury is in them essentially similar to that in the frog.

other hand, they may undergo progressive changes. The bodies may swell; mitosis may occur; and they may divide. This may take place in the cells of the fibrillar connective tissue and in the endothelium of the blood- and lymph-vessels. The new-formed cells may detach themselves from their original site and join the leucocytes as wandering cells. If there are small islets of lymphoid tissue, such as are widely scattered through the body (page 551), these may show hyperplasia, and appear as clusters of small spheroidal cells with large deeply staining nuclei and a small amount of cytoplasm. These clusters of small cells resembling lymphocytes are especially noticeable in the vicinity of the lymph channels near small blood-vessels.

Let us now look at the effect upon a living vascular tissue of injury inflicted in a different way.

Injury from Microorganisms.—Suppose we inject into the ear vein of a rabbit a small amount of a pure culture of a well-known and very common microorganism, Streptococcus pyogenes. Little masses of the living germ will enter the heart and be driven out again through the arteries in whose smaller twiglets or in the capillaries some of them will lodge as emboli. Here in the living tissues the bacteria may find good nutrient conditions and begin to proliferate, increasing so rapidly in number that they may distend the vessels in which they lie. If after twenty-four hours the animal be killed, and one examine the organs in which the bacterial emboli have caught and grown —in the liver, for example—one finds small blood-vessels here and there distended with bacteria. But the parenchyma and interstitial tissue about them appear to be intact (Fig. 60). If, however, the animal be allowed to live longer—say two or three days—before the examination, the condition of the tissue about the growing bacterial mass in the typical course of events shows marked and significant alteration. Immediately around the bacteria the nuclei fail to take the nuclear stains (Fig. 61); the cytoplasm is unusually granular or fallen into fragments. These are the marks of cell death, and from the situation of this area of dead tissue about the colony of growing bacteria we may infer—and the inference is confirmed by a host of tests and observations—that, in growing, the bacteria have set free in the tissue about them some chemical substance whose presence is incompatible with the continuance of the life processes in the liver cells, which, in fact, has killed them.

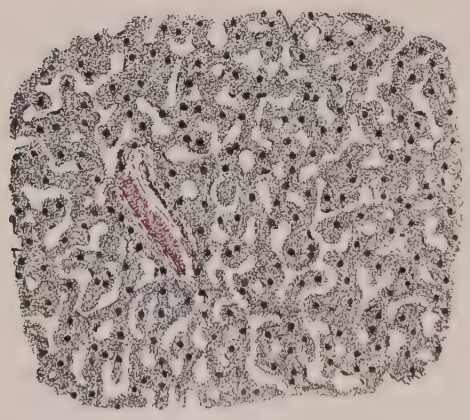


Fig. 60.—Bacterial Embolus in the Liver.

The bacteria have grown in a mass within the small blood-vessel. The liver cells in the vicinity appear unchanged.

But very soon the tissues near by show a different sort of reaction to this active poison set free upon the spot. Leucocytes gather on the borders of the necrotic area and may form a dense ensheathing mass about it (Fig. 62). If we look for the origin of these, we find that close outside the area of dead tissue and among the gathered leucocytes the smaller blood-vessels are dilated, overfilled with blood, and such marks of the emigration of leucocytes as a tissue removed from the animal and prepared for examination may show are unmistakable. Not infrequently extravasated red blood-cells and fibrin and a distention of the tissue spaces with fluid still further characterize the process as exudative inflammation.

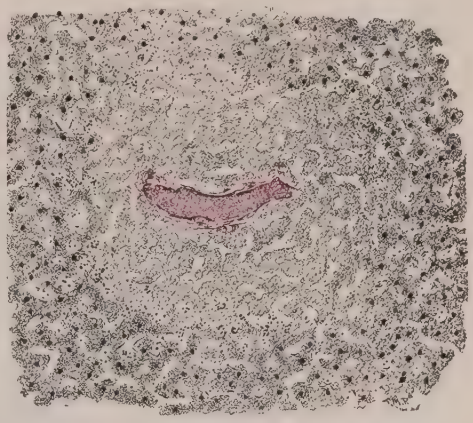


Fig 61.—Bacterial Embolus in the Liver, with Necrosis.

The bacteria are still largely confined to the vessel, but a few are outside. There is a zone of necrotic liver cells about the growing mass of cocci.

It was observed in the exposed mesentery or bladder of the frog that the leucocytes, once outside the vessels, wandered off in various directions in the tissues, some to the surface, some to the lymph-vessels, and some far from the veins or capillaries from which they emerged. Not so here. The extravascular leucocytes gather close in the border zone of the necrotic area or enter it. And we may usually see in the outer parts of such an area of dead tissue scattered leucocytes which are themselves undergoing changes indicating the death of the cell. They too have encountered the poison set free by the growing bacteria.

The changes which have just been described as the result of experiment in the animal are practically identical with those occurring in man as the result of accidental inoculation.

If the process continue, one may find on later examination that the dead tissue mass has softened through the action of proteolytic enzymes developed on the spot (page 126), the bacteria are scattered, and the whole central portion may be occupied by a grayish or yellowish grumous or fluid mass of dead cells, cell detritus, albuminous and fatty granules, bacteria, and leucocytes in various stages of necrosis and disintegration.

Such a localized result of exudative inflammation with death and disintegration of tissue is called an *abscess;* the material which it contains is called *pus.* (For a more detailed consideration of suppuration and the characters of pus see page 233.[1])

The changes by which, if the animal survive the formation of abscess, the active processes are brought to a standstill and repair is effected, we

[1] For a résumé of forms of exudate cells, with bibl., see *Helly*, Zieglers Beitr. 1905, xxxvii. 171.

need not now follow. But it concerns us here to appreciate that this is a type of one of the most important phases of the inflammatory process; a phase in which a poison produced in the body by the metabolism of microorganisms incites a complex train of active and passive tissue changes.

Instead of forming abscesses with softening of the tissue, the pus cells and other exudates may be distributed diffusely through the interstices of the tissues, forming a so-called *purulent infiltration.*

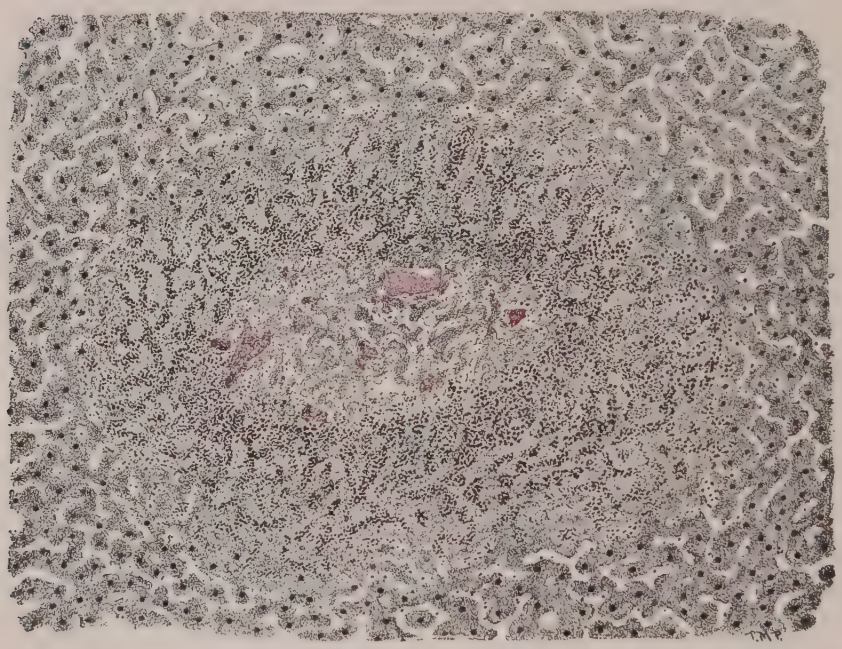


FIG. 62.—NECROSIS AND SUPPURATION IN THE LIVER FROM BACTERIAL INFECTION—EXUDATIVE AND NECROTIC INFLAMMATION.

The bacteria are scattered in masses, the liver cells about them are necrotic, while leucocytes have gathered in large numbers within the necrotic area. With slight further disintegration this mass of dead liver tissue and pus cells would form an abscess.

A narrow canal leading to a focus or area of inflammation is called a *fistula.*

In our study of illustrative phases of inflammation we now turn to the processes by which repair of injured tissues, after more or less involvement in the inflammatory phenomena, is brought about.

Resolution in Inflammation.—In many cases of exudative inflammation, after the subsidence of the active changes in the blood-vessels, the exudates are entirely, though often very slowly, absorbed, and the tissue returns to its normal condition; this is called *resolution.*

If many new connective-tissue cells have been formed, these may produce fibrils and thus a certain amount of new tissue may develop,

compromising the blood and lymph circulation, so that for a long time the site of the inflammation may be swollen and hard.

Under certain conditions, on the other hand—for example, in the case of a wound with loss of substance, or in an acute exudative inflammation of a serous membrane in which the surface is deprived of its normal mesothelial[1] covering, or in the healing of an abscess—a considerable amount of new tissue may be produced through the agency of old cells or of new cells formed in the inflammatory process.

We shall now consider the way in which repair of a wound or injury with loss of tissue is effected.

The Healing of Wounds.[2]

The way in which new inflammatory tissues are formed may be best understood by following the process of healing in a wound with loss of substance—for example, in a wound through the skin or a mucous membrane into the tissue beneath. At first there may be hemorrhage.

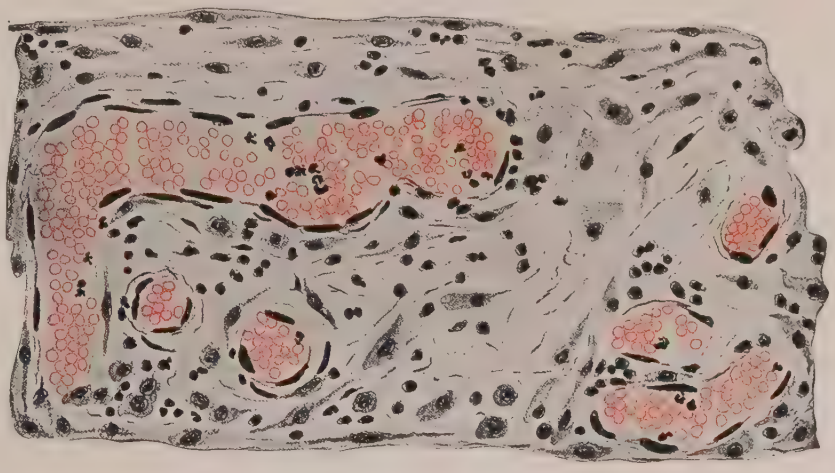


FIG. 63.—GRANULATION TISSUE.
From a healing abdominal wound. Early stage with very thin-walled blood-vessels, leucocytes, and young connective-tissue cells. There are few intercellular fibrils.

After this has ceased, the injury to the tissue, the unusual exposure of deep-seated parts, the presence of foreign substances, etc., may induce the same series of events which we have seen occurring in exudative inflammation with production of serum, fibrin, and pus. The blood-vessels dilate, the circulation becomes slower, serum transudes, and emigration sets in. Certain of the cells and fragments of intercellular

[1] The term *mesothelium*, suggested by Minot, is often used as a synonym for endothelium; but this is not correct. It should be remembered that the epithelium of the generative glands and of the convoluted tubules and looped tubules of the kidney is derived from the mesoderm, and that while these cells may be referred to as mesothelial in origin they certainly cannot be called endothelial. Minot himself used the term *endothelium* for the lining of blood-vessels, and applied the term *mesothelium* to the lining cells of the pericardial, pleural, and peritoneal cavities and the thick epithelium of the renal organs only. See *Minot*, Science, 1901, xiii, 481.

[2] For a general review of this subject, see *Wood, F. C.*, Keen's Surgery, Philadelphia, 1906, i, 348.

substance near the seat of injury may die, and in time be cast off or disintegrated, or dissolved and absorbed or otherwise disposed of by phagocytes (page 118). The tissue may become soaked and swollen by the transuded serum, and the connective-tissue cells in the vicinity may undergo proliferative or degenerative changes.

Granulation Tissue.—After a variable time, usually on the second or third day if all goes well, the surfaces of the wound may be more or less covered with tiny red nodules called *granulations*. These granulations contain numerous thin-walled blood-vessels which have sprouted out from the old vessels near the seat of injury, and around these a new

FIG. 64.—GRANULATION TISSUE FROM WOUND OF SKIN.
The walls of the blood-vessels are thicker, and intercellular fibrils are forming.

loose, succulent tissue is formed, largely, it is believed, from proliferation of connective-tissue cells. This is called *granulation tissue* (Fig. 63). On the surface of the granulations are usually pus cells in varying quantity, or the granulations may be more or less covered with dried exudate. The way in which the new blood-vessels form by protoplasmic sprouts from the old, and the manner in which connective tissue develops from older connective-tissue cells, have been already described in the section on Regeneration. Let it suffice here to say that the cells of the granulation tissue are at first mostly small and spheroidal or polyhedral, and are usually packed closely together with only a small amount of fluid intercellular substance. Presently some of the cells become larger and polyhedral, elongated, fusiform, or branched, and after a while a delicate, fibrillar intercellular substance makes its appearance about them and grows more and more abundant (Fig. 64). These larger, variously shaped cells, which appear to be formed out of the small spheroidal or indifferent cells of the granulation tissue, are usually granular, and the nucleus is generally large and distinct. Some of these larger cells which seem to be more or less directly concerned in the formation of intercellular fibers are called *fibroblasts* (Fig. 65).

As the granulation tissue grows, new, small, spheroidal cells are gathered by proliferation or by continued emigration. Some of these participate in the formation of the granulation tissue, while others, not finding conditions suitable for their further development, or even for their continued existence, die and pass off on the surface, together with some transuded fluid, as pus.

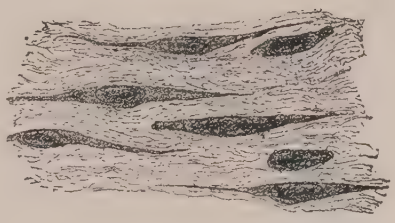


Fig. 65.—Fibroblasts of New Connective Tissue in a Healing Wound.

There are numerous new-formed intercellular fibrils.

The polynuclear leucocytes do not apparently share in the formation of new tissue. To what extent this new tissue is derived from old connective-tissue cells and cells of the endothelial type—the *macrophages* of Metchnikoff, the *polyblasts* of Maximow, the *clasmatocytes*,[1] or the *connective tissue mast cells*[2]—or how largely it may come from emigrated lymphocytes, assuming the characters of "plasma cells" (page 92), is not yet certain; but probably no one of these motile types of cells is actively concerned.

Cicatricial Tissue.—The new tissue gradually becomes more and more dense, the intercellular substance more abundant, while the cells decrease in number and become flatter and less conspicuous. The epithelium may

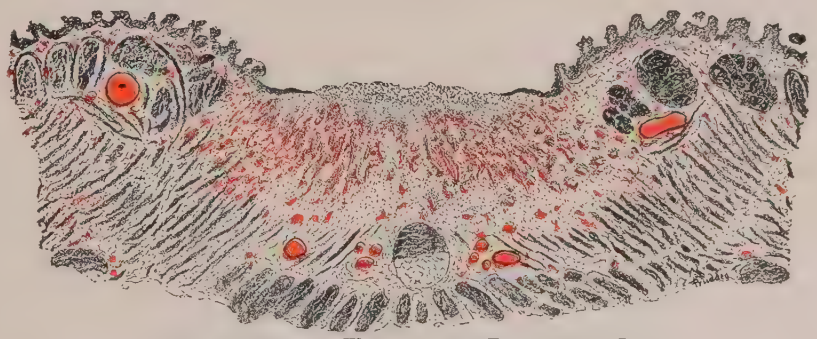


Fig. 66.—Healing Wound in the Tongue of a Dog.

There was loss of substance—muscle, fibrous tissue, and surface epithelium. The lost tissue has been replaced by the vascular granulation tissue, which is oldest and most dense in the deeper portion, while on the surface is a layer of tissue detritus, pus cells, etc., partly dried and forming a scab over the granulations. New epithelium is pressing forward from the old at the edges over the surface of the new-formed tissue.

now grow over from the sides, forming by mitosis from the old epithelium at the edges of the wound (Fig. 66), and finally cover the new vascular tissue. The new tissue, having at last undergone more or less

[1] Clasmatocytes (*Ranvier*, Arch. d'anat. micros., 1899–00, iii, 22) are cells found in the connective tissues in connection with inflammation. Their outline is very irregular, often with numerous long projections; the nuclear network is dense; the cytoplasm is spongy, and has embedded in it coarse refractile granules. The clasmatocytes are probably closely related to the fibroblasts of growing connective tissue. For experimental production of macrophages, see *Simpson, M. E.*, Jour. Med. Res., 1922, xliii, 77 (bibl.).

[2] Connective-tissue mast cells are cells which are frequently found in the normal tissues of some animals and in inflamed connective tissues of man. They have faintly staining, small nuclei with but little chromatin, and a cytoplasm which contains large numbers of granules staining deeply and metachromatically with basic stains. Apparently they play no important part in the inflammatory process.

shrinkage, with atrophy of the blood-vessels, consists of a dense, firm mass composed largely of fibrillar basement substance with a few flattened cells (Fig. 67); and with this, which is the *cicatrix*, the healing is complete. The cicatricial tissue in its shrinkage, as it becomes more fibrillar and denser, often brings about considerable distortion of adjacent parts.

Variations in the Healing Process.—Although in the production of new tissue, in connection with or following exudative inflammation, essentially the same processes are involved in all cases, there are yet very marked differences in the degree in which the different factors share. Thus the vascular and exudative phenomena may predominate and very large quantities of serum, fibrin, or pus collect, while the amount of new-formed tissue may be insignificant. The production of a large amount of exudate, particularly of pus cells—*suppuration*—usually marks the presence of microorganisms whose locally elaborated poisons complicate or retard the healing process.

Fig. 67.—Cicatricial Tissue from a Healed Wound.

In other cases the formation of new tissue is the dominant feature, and the production of exudates seems to be almost entirely subordinated to this end.

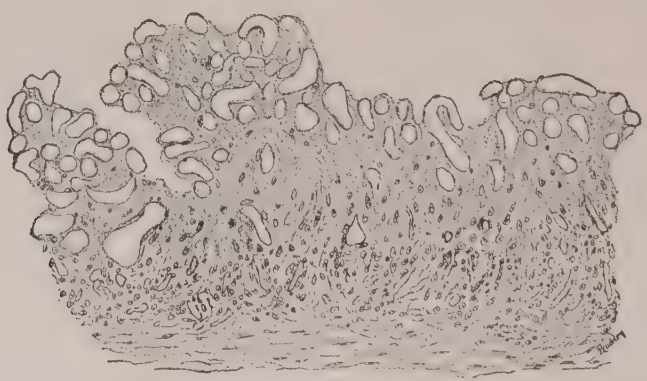


Fig. 68.—Exuberant Granulations.

From the inner surface of a granulating ovarian cyst containing pus. The tissue between the new capillaries is ill-formed, edematous, and with few cells, most of which have undergone fatty degeneration.

The process of repair which is complicated by exudative inflammation or effected only by the gradual formation of a considerable amount of new tissue, is called by surgeons *healing by "second intention."*

The distinction between healing by first and second intention, which is of practical importance in surgery, is, from the pathological standpoint, only a quantitative one; for the restitution of the parts to the healthy condition is in both cases brought about by exudation and prolif-

eration of cells usually under the influence of vascular changes, but in one case the latter changes are very slight, in the other more or less extensive.

There is much variation in the formation of granulation tissue. Thus, sometimes the body cells respond but feebly to the unusual conditions, and neither cell proliferation nor blood-vessel growth is active. On the other hand, the development of blood-vessels may be excessive, while other tissue formation lags. Under these conditions, loops and tangles of thin-walled, contorted new vessels may project from the granulating surface, while useful tissue formation remains in abeyance, or the new cells undergo fatty or other forms of degeneration (Fig. 68). The result of this disproportionate growth of ill-formed blood-vessels is the exuberant granulations ("proud flesh") which the surgeon frequently removes from unhealthy healing surfaces.[1]

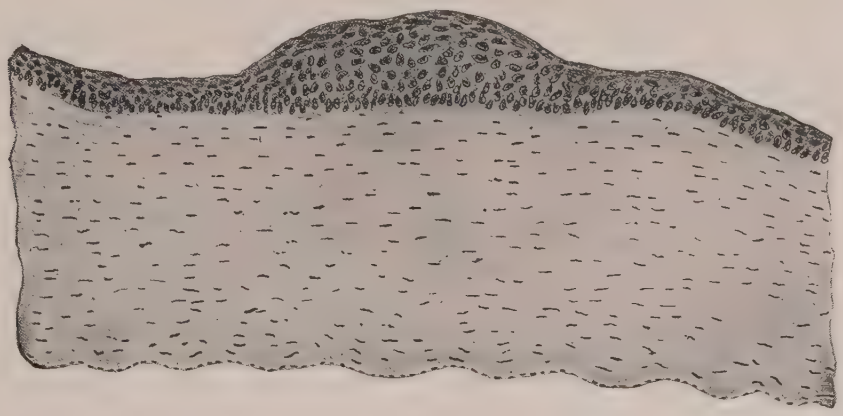


Fig. 69.—Regeneration of Epithelium over Superficial Wound of Cornea—Rabbit. The new epithelium has been formed in excess.

Cavities formed by abscesses or by necrosis in any part of the body may be filled up and their sides drawn together in a cicatrix, by the formation of a provisional mass of granulation tissue similar in character to that which grows in external wounds. So, similarly, cysts may be obliterated and ulcers partially filled and drawn into cicatricial healing. Large free surfaces, like the pleura and the peritoneum, may, through the intervention of granulation tissue, pass from the denuded condition of an active exudative inflammation, either with or without adhesions, into a condition which, though by no means a return to the normal, we yet designate as repair.

The so-called organization of a thrombus in a blood-vessel is brought about by processes practically identical with those which have just been described in the formation of new tissue in reparative inflammation in an external wound. The endothelial cells of the vessels and the connective-tissue cells in their walls proliferate, new blood-vessels develop by sprouts from the already existing smaller vessels in their walls or close about them. The new cells and new blood-vessels thus derived

[1] For a special study of granulation tissue, see *Reinbach*, Zieglers Beitr., 1901, xxx, 102.

gradually penetrate the clot, forming new connective tissue, which replaces step by step the fibrin and blood which are gradually softened by autolysis and absorbed or removed by phagocytes.

The part which the thrombus plays in its so-called organization is thus a wholly passive one. It acts only as a temporary supporting texture for the development of the new tissue derived from other sources which step by step replaces it.[1]

In the processes of repair by the formation of new tissues, the latter are often developed in excess, the overproduction after a time ceasing, when the normal condition is restored. Thus, if the epithelium be scraped from a small area on the front of the cornea the new epithelium which covers the injury is often heaped up in excess (Fig. 69).

Hyperplasia and Interstitial Inflammation.

Hyperplasia of the fibrous interstitial tissue of the internal organs and other parts of the body—as, for example, in the liver, kidney, heart, nervous system, etc.—is of frequent occurrence and is usually associated with changes in the parenchyma. In some cases the formation of fibrous tissue clearly follows evident and often acute inflammatory processes and bears the same relation to antecedent reaction to injury that the cicatrix in a healing wound does to the granulation tissue from which it is formed. In other cases it is associated with long-continued hyperemia—chronic congestion—of the organ involved. Again, gradual hyperplasia of the interstitial tissue takes place by the slow increase of cells and stroma, without evidence of an active cell proliferation or marked involvement of the blood-vessels. Finally, hyperplasia of the interstitial tissue may be, and probably usually is, secondary to damage to or atrophy of the parenchyma, as in the spinal cord after degeneration in nerve tracts or in the heart after damage to the muscle fibers; in the liver and kidney in connection with atrophy of the specific epithelial cells. In such cases it is often spoken of as *replacement hyperplasia*. These forms of fibrous-tissue hyperplasia will be considered with more detail in the sections dealing with the special lesions of the viscera. They have all been usually regarded as marks of inflammation. Some of them unquestionably are so; concerning others, doubt will continue until our knowledge as to their excitants considerably increases. In the meantime the term *fibrosis* is sometimes applied to the results of fibrous-tissue hyperplasia, though this is still most commonly included among the inflammatory processes.[2]

Those important phases of inflammation which are due to damage from special forms of microorganisms will be considered in detail in the chapter of this book devoted to the Infectious Diseases.

[1] While this view of the scaffold value of fibrin in repair of wounds and its chemotropic power on connective tissue and endothelial cells has long been regarded as settled, some recent observations of Baitsell suggested the direct transformation of fibrin into connective-tissue cells. Lambert has investigated the matter, using Baitsell's methods, but has found no support for the former's opinion. See, *Baitsell, G. A.*, Jour. Exper. Med., 1915, xxi, 455; 1916, xxiii, 739; *Lambert, R. A.*, Proc. Soc. Exper. Biol. and Med., 1916, xiv, 5.

[2] For a suggestive and interesting consideration of the relationship between inflammation and various forms of "fibrosis" see *Adami, J. G.*, Middleton Goldsmith Lectures, Med Rec., 1896, xlix, 361, *et seq.*

Special Phases of Inflammation.

The several phases of the inflammatory process which we have now considered are fairly typical of the reaction of the living body to various forms and degrees of injury. If we look at them together and seek to gather their dominant features, we find that the changes, varied as they are in character as well as in degree, are mostly of three kinds: first, those involving a greater or less amount of *degeneration* or *necrosis;* second, those involving local disturbances of the circulation, as well as alterations in the distribution and character of the fluid and cellular elements of the blood—*exudative changes;* and third, *regenerative, productive,* or *reparative* changes.

Of these three groups of alterations in inflammation those involving the blood-vessels and their contents are, in a clinical sense, most striking and characteristic, and to many seem to dominate the inflammatory processes. But in fact all are closely associated. The various phases of inflammation depend upon the nature and extent of the injury, the inherent reactive vigor of the cells, and the character and position of the tissue involved.

Special names have been attached to various forms of the inflammatory process, descriptive of the feature which from the particular standpoint of the observer seems most striking or important. Some of the names are descriptive of clinical symptoms, some express the duration or character or situation of the lesion, some seek to imply more or less well-founded views of the nature of the process. Thus among the forms of exudative inflammation, that in which the extravasated serous fluid is the most marked feature is often named *serous inflammation.* If fibrin predominate, it is called *fibrinous;* if associated with much blood extravasation, it is termed *hemorrhagic.* When the agencies are present which induce the necessary vascular changes and promote the emigration and gathering, and often the destruction, of leucocytes in considerable or large numbers, we have a *suppurative* or *purulent inflammation.* If much tissue death be associated with the process, it is named *necrotic inflammation.*

Again, if certain mucous membranes or mucous glands be subjected to the inciting agencies, they may respond by an overproduction of mucus as well as by an increase of death of cells; this is *mucous* or *catarrhal inflammation.* In inflammation of the mucous membranes fibrin intermingled with other exudate sometimes forms more or less well-defined and often tough pellicles or membranes upon the surface. This is called *pseudomembranous* inflammation. Finally, these various forms of exudate may be produced simultaneously, whence arise such compound designations as *seropurulent, mucopurulent,* etc., inflammation. Inflammation with the formation of new tissue is called *productive* or *reparative.*

Local inflammation, especially when incited by microorganisms, is often associated with systemic infection due to a distribution of the

inciting agents through the body. This condition will be considered in the chapter dealing with the Infectious Diseases (page 238).

Inflammation, especially of infective origin, is so frequently associated with degenerative changes in the more highly organized cells—the parenchyma cells—of organs that when these are conspicuously involved the term *parenchymatous inflammation* has been used. It is better, however, to hold the degenerations apart and consider them as associated but not identical with the inflammatory processes. Similarly the term *interstitial inflammation*, though very commonly employed, indicates a comparatively rare occurrence. That which is embraced under the term is usually an interstitial hyperplasia secondary to damage to the parenchyma cells of organs (page 116).

It has seemed wise to many to attempt to draw a sharp distinction between those phases of inflammation which involve only the degeneration of tissues or the redistribution of already formed tissue elements—serum, fibrin, and blood—and those phases which are productive or reparative. But while this attempt aims at the recognition of a biological distinction of fundamental importance, it encounters the great practical difficulty that both phases of the reaction of tissues to injury, the exudative and the productive, occur together, so that none of the named classes of inflammation represents a simple and unmixed form of tissue reaction. The important thing is to conceive, as clearly as our knowledge permits, the nature of the processes which underlie these various manifestations of disturbed cell function and their associated tissue alterations. Then the names may serve useful temporary ends at least without implying too much or concealing too little knowledge.

The Disposal of Foreign and Dead Substances in the Body—Phagocytosis—Autolysis.

It was stated at the beginning of this chapter that the injuries which lead to inflammation are extremely varied. The degree and character of the resulting inflammation are closely related to the inciting agents. We have already taken as general examples of the inflammatory response to injury, one in which there was a simple mechanical damage, and the other in which a more extensive and prolonged injury was effected by the presence of living bacteria.

While it is not practicable to classify the various phases of inflammation according to the character of their incitants it is convenient to consider by themselves the effects of animal and of vegetable parasites, among the latter especially the bacteria. In subsequent chapters, under the headings of Animal Parasites and of Infectious Diseases, we shall study the special phases of injury induced by these agents and the response which the living cells and tissues of the body make to their presence.

But there are many forms of injury to cells and tissues which, though not so extensive and striking as those which we have thus far considered in our preliminary survey of inflammation, are yet of great frequency

and importance. One of these we must now consider, namely, the presence in the body of foreign substances and of dead portions of the body itself. Here again, as in so many instances, we shall come upon physiological processes spurred to unusual activity by emergency demands upon them.

The Forms and Origin of Foreign and Dead Substances.—Under the conditions of normal life, as the tissues grow and perform their functions, worn-out cells die; as bone grows it is absorbed little by little to make room for the remodeling and growth of the larger structure; more or less constantly, floating matter in the air we breathe gathers in the respiratory organs. Under all of these conditions the dead cells, the hard bone, the foreign particles, are disposed of by certain lowly organized cells, leucocytes, lymphocytes, connective-tissue cells, endothelium and mesothelium, which are called *phagocytes*.

On the other hand, there are many conditions under which foreign material abnormal in quantity and character is formed in or enters the body and must be disposed of. Thus organic pigments in the form of irregular particles or crystals are formed in the body, such as blood and bile pigment. Many foreign substances in finely divided form in large quantities enter from without, especially in the respired air, such as coal, iron, stone, smoke, and various kinds of organic dust. In various ways larger bodies, slivers of wood, particles of metal, bullets, and, in injuries or during surgical operations, fragments of clothing, ligatures, sutures, fragments of sponge, cotton, gauze, jute, etc., may remain as foreign substances doing more or less harm and inciting in various degrees the phenomena of inflammation.

Finally, as the result of the greatest variety of injuries which lead to the necrosis of cells and tissues, such as mechanical damage, the action of corrosive poisons, excessive heat or cold, disturbances of circulation, various toxins, etc., the dead structures themselves become harmful to the living tissues about them, which respond in various ways to their presence, among others by certain forms of inflammation.

Let us see how the body cells and tissues comport themselves in the presence of alien substances and dead structures.

Disposal of Foreign Substances.—One of the simplest and most common of the phenomena of this class is seen in the disposal of pigment and other solid particles, whether introduced from without or formed within the body under various abnormal conditions.[1] When dusty air is breathed, whether of badly cleaned dwellings, places of business or assemblage, or in occupations involving the loading of the air with the dust of coal, smoke, iron, stone, tobacco, lint, hair, etc., in the aggregate large numbers of the dust particles enter the respiratory passages. Here sooner or later they are taken up by cells—phagocytes—and if the particles are colored they may be seen lying within the cytoplasm surrounding, but not within, the nucleus (Fig. 70). These cells may be the epithelium of the respiratory passages or of the air chambers of the lungs, or leuco-

[1] For a study of the removal of alien substances from the peritoneal cavity, see *Buxton* and *Torrey*, Jour. Med. Research, 1906, N. S. x, 5.

cytes which have wandered out upon the surfaces. Then a large part of the foreign particles, if these be not too numerous, are carried either on the lymph-currents or more frequently within cells into the lymph-channels, along which they make their way to the nearest system of lymph-nodes or -nodules or to the smaller areas of lymphatic tissue which are widely distributed in the lungs as well as elsewhere in the body (page 551). In these islets of lymphatic tissue or in the lymph-nodes of the lung the foreign particles both within and without the cells are deposited and may remain for an indefinite period.

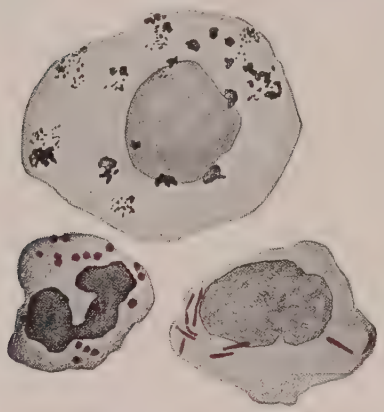


FIG. 70.—PHAGOCYTES.

The upper cell is epithelial from the lining of the air vesicles of the lungs. The pigment which it has ingested is coal dust from the air. The lower cells are leucocytes. One has taken in cocci, the other bacilli.

But the tissues in which they are deposited are not indifferent to the presence of any considerable accumulation of these alien substances. The connective tissue and endothelial cells swell and proliferate and new fibrils are formed inclosing the foreign material which may lie within the cells which brought them or be taken up by the new-formed or old connective-tissue cells or lie free in the interstices of the fibrils. Thus in the lymph-nodes and along the lymph-channels masses of dense fibrous tissue may be formed, shutting in the foreign material and compromising in varying degrees, sometimes completely destroying, the involved structures (page 555).

Similarly bacteria, which are also foreign bodies, may be taken up by phagocytes (Fig. 70) and destroyed within them by agencies presently to be considered, though the possibility that organisms may also be protected by such ingestion must not be lost sight of.[1]

If a mass of foreign particles is placed beneath the skin, or if at the seat of a hemorrhage insoluble blood pigment is formed in considerable amount, a similar process may be observed. The pigment is more or less taken up by leucocytes or other phagocytic cells which have wandered in. A certain amount of fluid exudate may collect. New cells are formed from the old connective-tissue cells and from endothelium, and new fibrillar stroma is formed which becomes dense and assumes the character of cicatricial tissue. In these changes the new-formed cells, as well as the leucocytes, are capable of moving from place to place, that is, may become wandering cells. We have then, in this relatively simple response to a small local injury, the presence of fine foreign particles, a definite form of inflammation. This is marked, not by the phagocytosis, but by the presence of leucocytes and a certain amount of fluid exudate, by the formation of new cells, and by the production of new tissue.

[1] *Rous* and *Jones*, Jour. Exper. Med., 1916, xxiii, 601.

When the alien material out of place in the living tissue is in the form of a loose-textured mass, such as sponge, fabrics, jute, catgut, etc., or is a blood-clot, its interstices become filled with fluid exuded from adjacent blood-vessels, with leucocytes which wander in, and with new

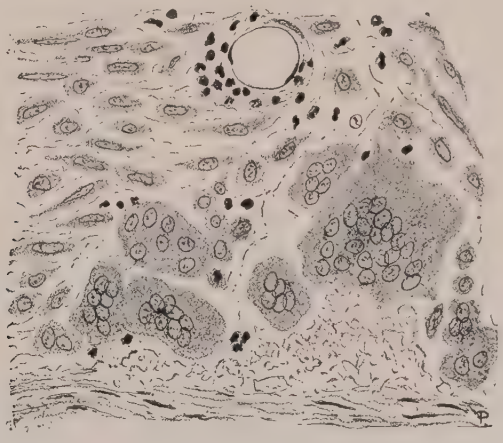


Fig. 71.—Giant Cells.
The giant cells are at the border of a layer of granulation tissue formed about a mass of dead fibrous tissue which is being absorbed.

connective-tissue cells derived from the surrounding parts and from the endothelium of neighboring lymp-vessels. Slender blood-vessels form from the old ones near by and penetrate the mass, and new connective tissue is developed, having the type of granulation tissue at

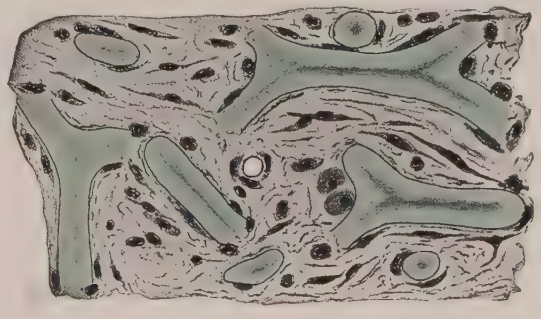


Fig. 72.—Fragment of Sponge in a Healing Wound—Three Weeks.
The sponge trabeculæ are not dissolved in the new-formed fibrous tissue, which has completely inclosed them.

first, then becoming denser. If the foreign substances are capable of solution, as is the case in the fibrin and cells of a blood-clot or of catgut, proteolytic enzymes[1] furnished by the leucocytes or other cells may dissolve them; or they become fragmented and the fragments are taken

[1] See *Wells*, Jour. Med. Research, 1906, N. S. x, 149 (bibl.).

up by phagocytic cells. These may be dissolved within these cells or may be transported to other parts of the body. Thus in the case of soluble material this may at length be entirely removed and its place taken by the new tissue which gradually assumes the character of cicatricial tissue.

If the foreign substance be insoluble or largely so, as in the case of bullets, needles, hair, cotton, sponge, etc., the new cells gather about the objects; there are often giant cells among them (Fig. 71), and new blood-vessels develop among these, leading to the formation of new connective tissue which may completely invest them (Fig. 72), forming at last a dense connective-tissue capsule. In this condition such foreign

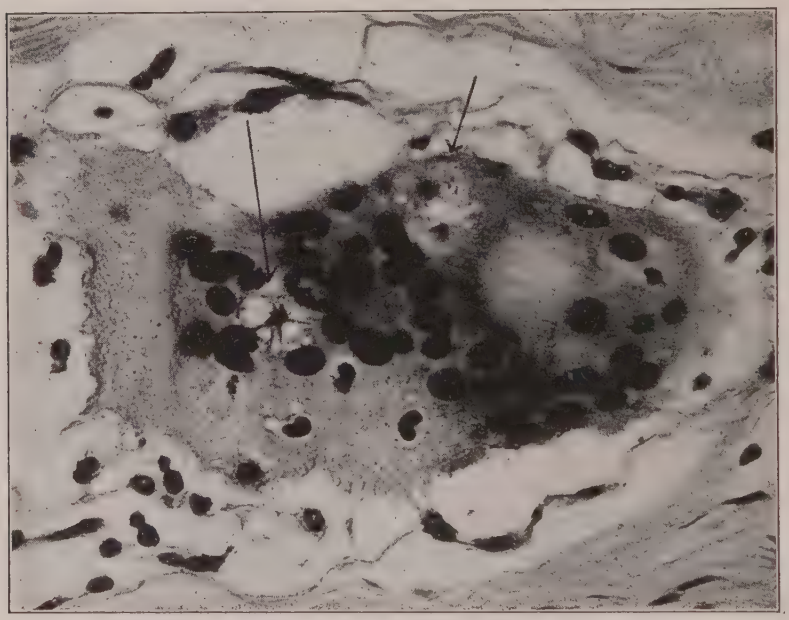


Fig. 73.—Stellate Bodies in Giant Cells. × 750.

objects may remain for long periods embedded in the body. If the masses of foreign bodies are small, so that the local reaction is limited and circumscribed, the new tissue often in a general way resembles a tubercle. Thus these new foreign-body tissue masses are sometimes called "foreign-body tubercles."

Giant Cells.—When foreign objects of considerable size—such as fat crystals, wax, cholesterin,[1] hair, cotton fibers, sponges, and various solid things—get into the living body, particularly if these be insoluble, in addition to the leucocytes and the new connective-tissue cells, there often form close about them large multinuclear cells called *giant cells* (Fig. 74). These are sometimes of extraordinary size and may have several score, even hundreds, of nuclei. They are apparently formed

[1] *Stewart*, Jour. Path. and Bacteriol., 1914–15, xix, 305 (bibl.).

either by the coalescence of new-formed cells derived from the connective-tissue cells or from old endothelium, or by the continuous division of the nuclei of a cell whose body continues to enlarge without dividing into separate cells.[1] These giant cells seem to be concerned in the attempt to dissolve the foreign substance and appear to have their prototypes in the multinuclear cells called osteoclasts (Fig. 75) which are concerned in the physiological absorption of bone during its development.

The Disposal of Dead Tissues.—The changes which we have now studied, through which alien substances are either removed from the body or rendered relatively harmless by processes which we must regard as belonging to inflammation, are similar to those by which the body responds to the injury of dead portions of its own tissue.

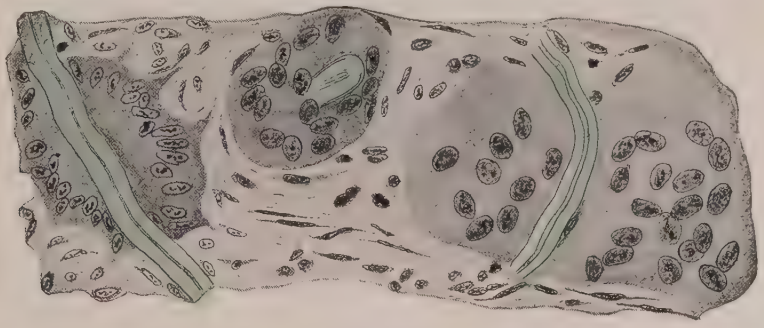


FIG. 74.—GIANT CELLS FORMED AROUND FOREIGN BODIES—COTTON FIBERS.
From a wound delayed in healing on account of the cotton fibers left in the dressing.

Thus, infarcts resulting from emboli, areas of tissue which have become necrotic from poisons or toxins, thrombi or masses of fibrinous exudate in the solid tissues or in the great serous cavities, are all virtually alien substances, and are harmful in various ways as foreign bodies are, and incite similar inflammatory phenomena. They may be in part removed by solution through the proteolytic enzymes,[2] or by phagocytosis; they may attract leucocytes (Fig. 76); they may lead to the proliferation of connective tissue and endothelial cells and of blood-vessels which penetrate them and form new tissue which finally replaces or encapsulates them. The so-called organization of a thrombus or of a pleural or pericardial or peritoneal exudate is not, as we have already seen, brought about directly by the aid of the structural or other elements in either the thrombus or the exudate. These are passive, except as they may aid in their own solution by autolytic substances which they furnish, while the new tissue is formed from neighboring cells and vessels.

Forms of Phagocytes.—There appear to be two most common forms of phagocytes in foci of acute exudative inflammations. First, and usually the most abundant, are the neutrophile polymorphonuclear

[1] Giant cells may be formed from epithelium under certain conditions. For a study of giant cells, with bibl., consult *Hektoen, L.*, Jour. Exper. Med., 1898, iii, 21; *Fuerst*, Zieglers Beitr., 1898, xxiv, 415; and *Buxton*, Studies from Department of Pathology, Cornell University, New York, vol. i.

For a study of peculiar stellate bodies in giant cells (Fig. 73), see *Wood, F. C.*, Proc. New York Path. Soc., 1915, xv, 63.

[2] See *Wells*, Jour. Med. Research, 1906, N. S. x, 149 (bibl.).

leucocytes—which so readily escape from injured vessels. The other type of the two more common phagocytic cells is usually larger than the polymorphonuclears and has a single, relatively large, rounded or irregular shaped nucleus. These mononuclear phagocytes of the second type are

Fig. 75.—Osteoclasts Dissolving Bone Lamellæ.
From a case of rarefying osteitis.

probably derived from connective tissue or endothelial and mesothelial cells or from lymphocytes, and have been called by Metchnikoff *macrophages*, while the smaller polymorphonuclear phagocytes are called *microphages*.

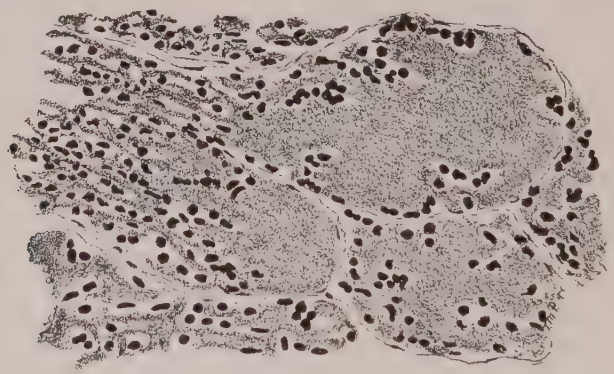


Fig. 76.—Fragments of Necrotic Muscle in Process of Absorption under the Action of Phagocytes.

While the performances of these two types of cells are not fully understood, it appears that the macrophages are especially concerned in the disposal of various protein and other formed elements which they ingest, such as fragments of fibrin and tissue detritus, dead parenchyma cells of organs, red and white blood-cells, etc. That the lymphocytic macrophages have any power to act upon living cells, as has been suggested by Da Fano,[1] Loeb,[2] and Murphy,[3] is doubtful.

[1] *Da Fano, C.*, Ztschr. f. Immunitatsforsch., Orig., 1910, v, 1.
[2] *Loeb, L.*, Jour. Am. Med. Assn., 1915, lxiv, 726.
[3] *Murphy, J. B.*, Proc. Nat. Acad. Sc., 1915, i, 435.

On the other hand, the polymorphonuclear leucocytes—microphages—are drawn to and ingest and destroy various kinds of microorganisms, especially the bacteria.[1]

While we have thus far considered certain special cells, leucocytes, lymphocytes, and derivations of connective-tissue and endothelial cells, as the most common phagocytic cells in inflammation and repair of tissues, we should not lose sight of the fact that other types of cells also are capable of assuming this rôle.[2] Thus the epithelium of the mucous membranes of the air vesicles of the lungs, of the liver, kidney, and other organs, frequently and under the most varied conditions ingest particles of foreign material.

The Mode of Action of Phagocytes.—As to the processes by which the phagocytic cells convert into soluble and other forms the substances which they ingest there is still some difference of opinion, though the so-called intracellular digestion and the autodigestion of tissues have been the subject of much painstaking research.

Recent studies[3] indicate that each of the two types of phagocytes above designated is characterized by a distinct proteolytic enzyme through which its destruction of organic substances is effected. The enzyme of the polymorphonuclear leucocytes is capable of proteolytic digestion in the presence of a neutral or alkaline reaction, but not in an acid medium. This enzyme is called *leucoprotease*. The larger mononuclear cells, on the other hand, the "macrophages" or "macrocytes," which appear to be especially concerned with the ingestion and destruction of cellular and other formed elements, contain an enzyme active in the presence of a weak acid, but inactive in an alkaline, medium. This enzyme is called *lymphoprotease*. Neither of these ferments is bactericidal.

Blood-serum inhibits the action of leucoprotease, and lymphoprotease is not active in an alkaline medium. Hence, the living tissues of the body are not digested by the leucoprotease, which is active only within the bodies of the microphages, where it is free from the inhibiting action of the serum, while the alkalinity of the blood plasma protects the tissues from the action of the lymphoprotease. It is apparently the action of these proteolytic ferments, present in considerable quantities either within or without the cells or both, in foci of exudative inflammation, which leads to the softening of tissue which characterizes abscesses and which, in part at least, brings about the more gradual solution of necrotic tissues, fibrin, pneumonic exudate, etc.[4]

The action of microorganisms, especially the bacteria, as incitants of inflammation through the injury which they cause, and the ways in which the body reacts to and disposes of them, through the action of

[1] For a consideration of the ways in which bacteria are destroyed by leucocytes, see pp. 187 and 204. See also *Buxton* and *Torrey*, Jour. Med. Research, 1906, N. S. x, 5.

[2] See, for a study of this question, *Bartlett* and *Ozaki*, Jour. Med. Research, 1917, N. S. xxxii, 139.

[3] *Müller, Fr.*, Verhandl. d. Kong. f. inn. Med., 1902; *Opie, E. L.*, Jour. Exper. Med., 1906, viii, 10, 536; *Jochmann, G.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, i, 1301.

[4] *Wells*, Jour. Med. Research, 1906, N. S. x, 149; and *Levene*, Jour. Am. Med. Assn., 1906, xlv, 774, 866.

phagocytes or otherwise, will be considered later under the heading of Infectious Diseases.[1]

It should be borne in mind, in considering the varied and complex performances of phagocytic cells under abnormal conditions, that these are only the manifestation in exaggerated form in the presence of emergencies of physiological capacities of many kinds of cells. To Metchnikoff especially we owe our knowledge of the phagocytic powers of cells in general. In such lowly organisms as ameba and in many other cells throughout the animal kingdom, he has shown that through ingestion and intracellular digestion cells not only are nourished but protect themselves against harmful agents and influences.[2]

Autolysis.—All the manifestations of cell life are brought about by the breaking down or disintegration of chemical substances in the cytoplasm by processes akin to those of combustion. It has long been believed that this was exclusively a property of living matter. But it has recently become known that dead cells also under certain conditions have the power of self-disintegration. This is called *autolysis*. It takes place in the absence of microorganisms through the action of which organic material is decomposed in the commoner processes of putrefaction. Thus portions of fresh organs removed from the body with the avoidance of bacterial contamination, that is, in a sterile condition, if immersed in chloroform water, or toluol, or other substances which do not cause alterations of the tissue but do prevent the growth of microorganisms, and kept at about body temperature, undergo gradual softening. This softening is accompanied by definite structural changes in the cells. The nuclear chromatin disintegrates or goes into solution; the cytoplasm degenerates, chemical analysis showing products of the disintegration of protein substances. The changes are analogous with those taking place in organic material, cells, etc., under the influence of the digestive enzymes, pepsin and trypsin, but are due not to these but to other enzymes belonging to the cells themselves (page 117).

It appears, for reasons into which we cannot enter here, that the proteolytic enzymes active in the autolysis of dead tissues are present in the living body and are probably concerned among other things in the gradual removal of dead and enfeebled structures as these become defective, useless, or harmful. It has been shown that the vigorous, living cells, in spite of their autolytic powers, probably maintain their integrity through the presence in the body-fluids of substances antagonistic to the autolytic enzymes. Thus it appears that under normal conditions a very nice balance exists between the autolytic enzymes and antagonistic substances within the body. Under a variety of abnormal conditions, such as diseases of the respiratory and circulatory systems, phosphorus poisoning, and infectious diseases,[3] autolysis may be in a marked degree exalted.

[1] For a consideration of Ehrlich's hypothesis as to the way in which bacteria are destroyed in the body, see page 202.

[2] See *Metchnikoff*, Comparative Pathology of Inflammation, English trans., 1893; and Immunity in Infective Diseases, 1905. Consult also page 224.

[3] *Flexner*, Tr. Assn. Amer. Phys., 1903, xviii, 359; and *Dernby, K. G.*, Jour. Biol. Chem., 1918, xxxv, 179.

It is probable that the autolytic substances in the living body are important not only in disposing of damaged or dead or harmful tissues, but also in the protection of the body against invading microorganisms through their destruction (see Immunity and Bacteriolysis, pages 191 and 206), or by their share in the elaboration of substances which antagonize the action of their toxins (see Antitoxins, page 195).[1]

Survey of the Inflammatory Process and its Significance.

Inflammation a Modification of Physiological Processes. — If now, from the vantage-ground which we have won by our study of various typical phases of inflammation, we seek to gain an insight into the forces which dominate the varied processes, we note at once that from first to last the cell and tissue performances in inflammation, however exaggerated or perverted, are only the expression of physiological capacities which belong to the structures involved. Thus the contractions and dilatations of the vessels are paralleled in health. The exuding of fluids through their walls occurs by processes akin to those by which blood pressure, osmosis, and selective filtration in endothelial cells maintain the initial circulation into and through the tissue spaces. Emigration is a physiological process which we find excessive here, because there are structural alterations in the walls of the vessels which permit a freer exit of the cells, and because there are also present new and active chemical agents which, just as in normal conditions though in exaggerated fashion, excite and control the movement and direction of the leucocytes. The healing processes, complex as they seem to be, are actually but a rehearsal under the unusual and often difficult conditions of cell and tissue formation, which is characteristic of the normal period of development. Phagocytosis is a factor of the greatest importance in the normal as well as in these abnormal performances of the body cells.

The degenerative phenomena, among which must be reckoned the formation of fibrin, are, as we have seen, incidental rather than primary factors in inflammation.

Thus in all the manifold manifestations of abnormal cell performance in inflammation we find no new functions, no new cell capacities.

The Significance of Inflammation.—We are now brought face to face with the final question: What does inflammation mean?

In those phases which involve the repair of wounds and the regeneration of lost tissues it is not difficult to recognize conservative and beneficial processes. But how is it with those phases of inflammation in which the blood-vessels are largely involved and exudates formed—serum, fibrin, and pus? Are we to be contented here with a simple summary of the phenomena and with the recognition that these are the results of exaggerated or physiological cell and tissue performances in the face of injury? Or, on the other hand, is there reason for the belief

[1] For an interesting résumé of autolysis with bibl. see *Levene*, Jour. Amer. Med. Assn., 1906, xlvi, 774, 866. For a fuller consideration of the subjects dealt with in this chapter consult the general pathology, Les processus généraux, of *Chantemesse* and *Podwyssotsky*, Paris, 1901, or *Wells*, Chemical Pathology, 5th ed., Philadelphia, 1925.

that these abnormal manifestations of cell life in the presence of an unusual and deleterious environment may, after all, be in the main conservative in their nature, and, even as normal cell functions do, tend—within the limitations of an emergency—to the welfare of the individual?

The Rôle of the Exudates.—In the hope of gaining some light upon this question let us look a little more closely at the part which the exudates play in exudative inflammation; and first at the leucocytes.

The Leucocytes.—It was through the painstaking and brilliant studies of Metchnikoff[1] that attention was directed to the importance in this connection of comparative studies upon the comportment of lower forms of life in response to injury.

It was found that ameba, one of the simplest of organisms, when cut in two may undergo complete restitution of the part containing the nucleus, provided the latter be uninjured. The remaining portion may live for a time, but ultimately dies. Furthermore, it was found that ameba and other lowly forms of living beings are capable, by the use of their simple digestive processes, of destroying microorganisms which are taken into their interior and which might otherwise damage or kill them. Thus it was established that the digestive mechanism may become protective in lowly organized cells.

Rising in the scale of living beings, it is found that in forms in which considerable differentiation of some of the cells has taken place, whether there be a distinct circulatory apparatus or not, certain other cells are left in a more primitive state; these are phagocytic and can ingest or otherwise destroy deleterious material.

When we come to man and other warm-blooded animals, it is upon the leucocytes which have retained so many of the capacities of undifferentiated protoplasm that attention is especially concentrated. It has been found, as we have already seen, that the movement of leucocytes may be directed toward (sometimes from) chemical substances set free in their vicinity. This chemotaxis is frequently manifested in the vicinity of dead cells or tissues which are the seat of destructive metabolism. But it is especially in relation to microorganisms of various forms that chemotaxis in the leucocytes is of the highest significance to us here.

Highly virulent microorganisms may for a time repel the leucocytes, probably through negative chemotaxis, but these may later approach. On the other hand, leucocytes most often migrate toward bacteria which have gained entrance to the body. It has been proved that leucocytes, especially the polynuclear neutrophiles, and frequently large mononuclear forms, may take into their interior and destroy living bacteria. Dead bacteria also, as well as other inert material, they can engulf and destroy.

The Body Fluids.—This capacity of leucocytes and other mesodermal cells—endothelia, etc.—to take up living bacteria and kill and digest them was persistently and ably urged by Metchnikoff and his pupils as the chief protective agency in the body against bacterial incursions, and

[1] *Metchnikoff*, Comparative Pathology of Inflammation, Eng. trans., 1893.

to these observers all the other phenomena of inflammation formerly seemed of secondary importance. But it was soon shown that this extreme view is not correct. For it was demonstrated by many observers that the body fluids, especially blood-serum, are capable of killing bacteria with which they come in contact. When, however, this remarkable quality of the body fluids was investigated, it was found that it is most pronounced under conditions which involve the breaking-down of leucocytes or the liberation of the destructive substances into the fluids. It was possible now to demonstrate that the leucocytes do, in fact, contain a germicidal protein substance or substances. These substances, which appear to be closely associated with or related to nucleinic acid, have been called "alexines" or "protective proteins."[1] It has been further demonstrated that while the eosinophile cells may move toward bacteria, they are not phagocytic, but may set free granules which appear to favor the destruction of the germs.

It thus appears that the earlier view of the almost exclusive importance of phagocytosis is not sustained, but that even more than in the action of living phagocytes the protective agencies are to be sought in the body fluids. But it is also clear that the protective capacities of the body fluids are the result of cell activities, as indeed might have been inferred in advance of the long line of careful experiments which finally led to the demonstration.

The importance of this protective power of the body-cells and body fluids is not exhausted with their germicidal action. For not less significant is the rôle which these may assume in the establishment of other phases of immunity to the incursion of microorganisms. This will be considered later in the general survey of the infectious maladies (page 191).

If now one seek for ways in which the other exudates, serum, and fibrin may be useful to the individual, it is obvious that in the dilution of locally engendered poisons and in their removal from a vulnerable region the fluid may at times be beneficial. Fibrin, too, by closing inflammatory foci, through temporary adhesions, or by the sealing of absorbent surfaces, may limit the extension of injurious agents, as is so frequently the case in local infectious injuries in the peritoneal and pleural cavities. That the regeneration and repair of tissue which may be associated with or follow the more active phases of inflammation are, as a rule, beneficent, is not doubtful.

There is, of course, another side to the matter. For new cicatricial tissues which have formed in the process of repair may be so situated as to cause serious impairment of functional performance or even fatal strictures. The gathering of leucocytes, too, may be so excessive and their proliferation so extreme as to lead to delayed healing or to serious exhaustion from suppuration. But notwithstanding these irregularities and failures there seems to be good reason for the belief that, on the whole, the processes involved in inflammation are conservative, and, within the limitations which may be set by the varied and changing conditions of injury, tend to maintain the welfare and sustain the life of the individual.

[1] For further consideration of this subject see page 191.

CHARACTERIZATION OF THE INFLAMMATORY PROCESS.

The general conception of inflammation which we have just set forth looks beyond the gross manifestations of disordered function and altered structure, by which it was originally marked, and beyond the complex and varied expressions of aberrant cell activities, with which our later science has mostly dealt, to the fundamental qualities of living substance. And thus at last, with the heart of the subject in view, a characterization of inflammation becomes possible which is suggestive and useful, though it may not indeed be final. Perhaps among many such characterizations, that of Adami[1] is on the whole the most clear and precise, and with him we may at present wisely consider inflammation as "the local attempt at the repair of injury." The fundamental conception upon which this characterization is based is that inflammation is an emergency measure incited by injury, in which the body adapts to unusual ends as best it can mechanisms and powers normally maintained for other purposes.

This view of inflammation, however much it may be modified as our knowledge grows, recognizes a far-reaching significance in the complex processes involved. And while throwing light upon the practical problems of the physician, it points the way to a broader conception of other abnormal conditions in which also the adaptation of physiological cell capacities to new conditions seems to furnish a clew to many manifestations of disease as yet but little understood.[2]

Now that we have gained a conception of the inflammatory processes in general and some suggestions as to their significance, it does not seem necessary to enter here upon a detailed description of the variations which they present, since these are largely influenced by the character of the inciting agents and by the situation in which they act. Such details as may fall within the scope of this work are given in the section dealing with microorganisms as inciting factors in disease, and in the part dealing with the lesions of special organs.[3]

The Experimental Study of Resorption of Foreign Material, Phagocytes, etc., in Inflammation.

Aside from clinical material illustrating the healing of wounds and various phases of repair from the lower animals, one may obtain by very simple operations, to be done with local or general anesthesia, many valuable series of demonstrative lesions.

[1] For a fuller consideration of inflammation from the point of view which in general is here adopted, one may consult the excellent article on "Inflammation" by *Adami* in Allbutt's System of Medicine, 1905, i, 702.

In *Thoma's* work on General Pathology, vol. 1, is a clear exposition of the various processes concerned in inflammation, with a fuller recognition than is commonly accorded to them of the mechanical factors involved. In both of these works the more important bibliography may be found.

For bibliography and critical résumé of studies on pathological organization, inflammation, etc., see *Borst*, Lubarsch and Ostertag, Ergebn. d. allg. Path., 1897, iv, 461. See also under Regeneration, page 86.

[2] Consult, for a clear and comprehensive view of adaptation in pathological processes, *Welch*, Tr. Cong. of Am. Phys., 1897, iv, 284.

[3] For a systematic and extensive résumé of inflammatory phenomena, phagocytosis, chemotaxis, emigration, diapedesis, protoplasmic poisons and irritants, the nature of exudates, and the general physical chemistry of the cell, with extensive bibl., see *Heinz*, Handbuch d. exper. Path. u. Pharmakol., Jena, 1904, i.

Phagocytes.—The injection of 1 per cent. agar—such as is used for bacterial cultures, which fluidifies at about 40° C. and becomes semisolid on cooling—into the anterior chamber of the eye or into the subcutaneous tissue of the rabbit gives most instructive pictures of absorption and phagocytosis. Phagocytes of connective-tissue origin bring about the solution of the mass and permeate it. If the agar be colored with Berlin blue in the form used for blood-vessel-injection masses, the phagocytes may become more or less filled with the blue granules as absorption proceeds. In the absorption from the anterior chamber in dark-colored rabbits the origin of the phagocytes in the iris is revealed by their pigmented character. Giant cells are often formed in this process, aiding in the resorption.

The action of phagocytes in disposing of foreign material in the lungs may be seen by making intratracheal injections of a watery emulsion of lampblack or finely powdered charcoal in rabbits. The pigment particles will be found both free and within epithelial phagocytes in the air vesicles within a few days. The animal should be sacrificed and the lungs filled with formalin solution or alcohol through the trachea (page 1237), after which the tissue is embedded and sectioned.

Very instructive studies may be made of the disposal of insoluble foreign bodies by the implanting of small fragments of cotton, jute, elder pith, etc., beneath the skin, and their removal after varying intervals.[1]

Practical Study of Exudative Inflammation on the Living Frog.

In the study of exudative inflammation it is of the highest value to see the phenomena of emigration, diapedesis, etc., in the living animal. The curarized frog is best adapted for this purpose,[2] and either the mesentery or the bladder affords much clearer pictures than the tongue or the web, which are sometimes recommended.

The Mesentery.—In a fully curarized frog an incision is made through the skin along the abdomen in the axillary line, care being taken to avoid or ligate a large vein which usually crosses the line of incision. The abdominal wall is then cut through in the same line, and a loop of small intestine drawn out, care being taken to bring out only as much as may be necessary to expose over the glass window of Thoma's frog plate[3] (see Fig. 77) a small area of mesentery. The loop may be fixed by short pins passed through the superficial layers of the intestine into strips of cork which are crowded in beside the raised glass window. The exposed loop should be irrigated with 0.75 per cent. saline solution which may be made to trickle over the part from a reservoir through a glass cannula held by the cannula-holder (see Fig. 77). Peristaltic movements of the intestine sometimes cause the field of observation to shift and stasis may occur if the loop be drawn too tightly. But through a little attention to adjustment from time to time difficulties may be reduced to a minimum. For long observations a cover-glass may be laid upon the loop under which the irrigation proceeds.

In this way observations may be made on arteries, capillaries, and veins, extending over several hours. Long focal distance, high-power lenses may be used.

The Bladder.—The bladder of the frog is a bilobed organ opening into a cloaca just within the anus and common to it and the intestine. To expose the bladder an incision is made in the axillary line along the lower half of the abdomen, including the skin and the abdominal wall. The bladder frequently prolapses at once to a moderate extent through this opening. Now a glass cannula is made with a tapering tip with the

[1] For a full exposition of methods of experimental pathology relating to inflammation, see *Heinz*, Handbuch d. exper. Path. u. Pharmakol., Jena, 1904, i, 255.

For many suggestive studies in phagocytosis, see *Metchnikoff's* Immunity in Infectious Diseases. Consult, for the technique of studies on absorption from the peritoneum, *Buxton* and *Torrey*, Jour. Med. Research, 1906, N. S. x, 5.

[2] For the use of curare see page 46.

[3] Thoma's frog plates are of three forms, adapted for the study of the tongue, the mesentery, and the bladder or lung. They are plates of brass covered with hard rubber in which glass windows are set so that when put on the stage of the microscope the light passes up through the exposed organ to the eye. They are provided with cannula-holders for irrigation with physiological salt solution and with pipes for carrying away the waste irrigation fluid. The three forms of plate are shown in Fig. 77.

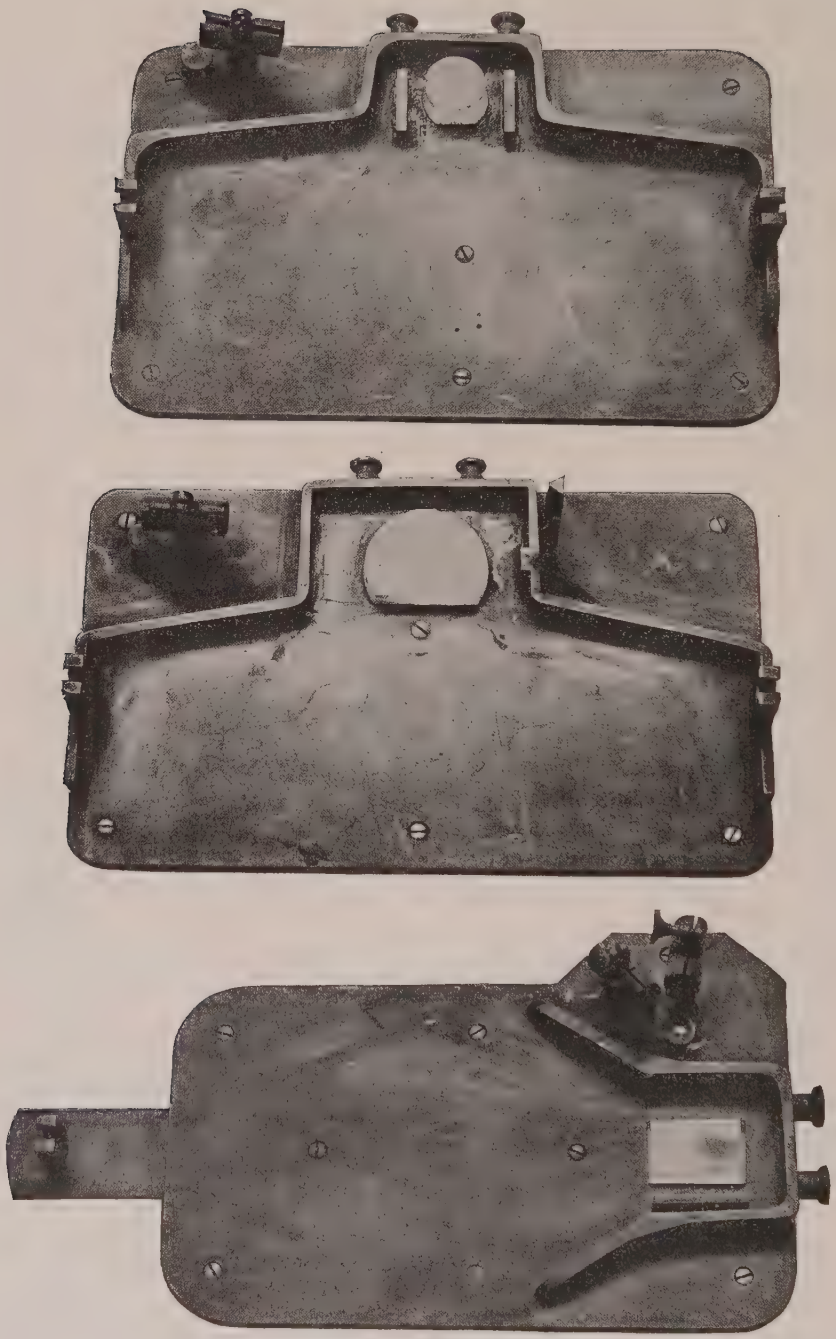


FIG. 77.—THOMA'S FROG PLATES.

The upper plate is adapted to the study of the circulation in the mesentery. The middle plate is for the bladder and lung. The lower plate is for the tongue.

tip for about half an inch bent to an angle of about 45° to the axis of the tube. The tube should be large enough to pass the anal orifice with difficulty except at the tip and along the bent portion.

A thread is now passed through the skin just behind the anus, the ends being left free. The cannula and a short length of flexible rubber tubing slipped over the larger end are filled with 0.75 per cent. saline solution, this being retained by a clip on the tube. The bent point of the cannula is now inserted into the cloaca and its tip carried forward into the base of the bladder and fastened in place by the thread. The frog is laid on its back on the Thoma plate adapted to the bladder and lung (Fig. 77). The rubber tube is attached to a slightly raised flask so that the salt will siphon into the bladder under a very low pressure. Now if the clip be released the bladder will appear in the opening of the abdomen and will be pressed out as a transparent bag by the salt solution over the glass window in the plate. Great care should be taken to avoid more distention of the bladder than is necessary to keep it spread over the glass, since the circulation is very easily disturbed or interrupted. A cover-glass may be laid upon the bladder or held in place over and touching it by an upright attached to the plate for this purpose, and irrigation with salt solution started and maintained.

If the circulation is compromised one should see that the base of the extruded portion of bladder is not pressed upon by the abdominal walls; that it is not overfilled and is not pressed too much by the cover. By attending to those points in a frog not over-curarized one may maintain the circulation for hours. Since the wall of the bladder is very thin, consisting of little else than the almost invisible epithelial lining, a membranous connective-tissue wall reinforced here and there by slender bundles of smooth muscle cells, and the blood-vessels, one secures in this organ pictures of the blood-vessels of incomparable clearness and may study the minutest phases of the circulation and its disturbances, emigration, etc. The contraction of the muscle bundles brings about occasional shifting of the field, but this is not usually a serious drawback to continuous observation even with high-power lenses.

On the whole, though slightly more difficult to prepare, the bladder is to be preferred to the mesentery for studies on the minute phenomena of emigration, diapedesis, hemorrhage, etc., and it is admirably suited to the study of the local effect of drugs, such as adrenalin, on the circulation.

In neither the mesentery nor the bladder is it necessary to injure the organ further than is inevitable in the preliminary operation and exposure, in order to incite the inflammatory phenomena in the vessels. In both organs the course of the emigrated leucocytes may be followed through the interstices of the tissues after they have left the vessels. It is most instructive after the observations on the living animal are completed to pith or decapitate the frog, fill the bladder with a fixative such as Orth's fluid, in which the organ after ligating is placed, and finally to scrape off the epithelium, stain with hematoxylin and eosin, and mount pieces of the wall in balsam for study.

The Lung.—The circulation in the lung and various phases of its disturbance may be studied in the living frog by the use of the Thoma plate especially adapted for the bladder. The preliminary operation is made in the axillary line, the long incision reaching forward to the axilla. A cannula tapering to one end so as to pass between the folds of the glottis for five or six mm., but not to slip further in, is tied in place by a thread through the snout of the curarized animal. A flexible rubber tube over the free end of the cannula, which extends a couple of centimeters beyond the snout and is controlled by a clip, enables one to blow into the lung and force it out through the incision. The inflation should not be excessive and the base of the lung should not be constricted. The animal is placed on its back upon the plate with the distended lung over the glass window and irrigated in the manner above indicated for the bladder. The picture of the circulatory districts of the single-sac lung with the blood shooting through the rich capillary network and entering the veins is most interesting and important for one who would appreciate the significance of lung lesions involving, as most of them do, disturbances of the circulatory mechanism.

CHAPTER VI

ANIMAL PARASITES.

INTRODUCTION.

The relations between man and a host of parasitic plants and animals have an important bearing upon many of his activities. The opinion has been held, for example, that the Greeks were conquered much less by Roman military power than by the ravages of malaria; and it is unquestioned that the useful occupation of tropical regions by the Caucasian race has been possible only through the hygienic control of parasitic invasion, and the consequent decrease of malaria, yellow fever, dysentery, and other diseases. The improved conditions in Porto Rico, as an instance, have been due more to the hygienic campaign against the hookworm than to any other factor. Of late, many of the advances gained in hygiene have been obtained by experimental investigation; for example, the fixation of the transmission of malaria and yellow fever on the mosquito, of typhus on the louse, of plague on the flea. There has thus been a renewed interest in parasitism, increased recently by the varied and novel epidemics of the present time.

Parasitic plants and animals may be classified as ectoparasites and endoparasites. The first live on the surface of the body, the latter in its interior. Of the plants, the moulds which induce skin lesions are the best examples of the ectoparasitic, the bacteria and yeasts of the endoparasitic type. Both of these are considered in detail in subsequent chapters. In the animal kingdom, the ectoparasites, such as the fleas, and mosquitoes, are also classed as temporary for, after obtaining such food as they desire from the human host, they may abandon their prey for other purposes. The endoparasites as a group are much more likely to be permanent; such are the various intestinal worms, which may pass their entire existence in the alimentary tract of an individual unless changing conditions drive them out. A good example of this is the cosmopolitan worm, *Trichuris trichiuria*, which undoubtedly remains in the intestines of its human host during its entire life, chiefly because it is not inimical to health. Other types, such as amebas or the malarial parasite, while causing serious or even fatal lesions in some instances, in others may be gradually eliminated either by healing of the parasitic lesions, or by destructive action of the natural defences of the blood and cellular organs.

The action of the parasite on the host may be of the most varied nature. Some are harmless; others, such as the worms, vary greatly, passing from the harmless Trichuris just mentioned to the Anchylostoma or Bothriocephalus which may incite fatal anemia by their poisons. Some act by invasion of the body, as the Trichinella; others act destructively on specific cells, as the malaria plasmodium on the red corpuscles;

others, by their general invasion of the organism and the toxic products which they give off, set up processes often leading to a series of apparently independent diseases, the best example being the Treponema, whose relationship to paresis and tabes has but recently been established. Still others, while relatively harmless may, as Ascaris, cause death by mechanical means, the invasion of the trachea inducing suffocation, or that of the bile-ducts setting up a serious and sometimes a fatal train of lesions.

The action of the host on the parasite is of great biological interest. Unquestionably many human parasites originally infested animals and have only comparatively recently invaded man. Thus, there are many instances of incidental or facultative parasites, frequent in animals and occasional in man. The *Balantidium coli* is frequent in swine and rare in man; the same is true of the *Dipylidium caninum*, a dog tapeworm. Many of the worms have closely related forms found in fresh water which are not at present parasitic, though the possibility of their becoming so awaits only a suitable host.

The influence of the host is also shown in the fact that many of the most highly adapted forms show evidence of devolutionary processes. The *Tænia saginata* of the human intestine is unsuited for any situation except that in which it is now found. The suckers of the scolex which retains the worm in the intestine, and the highly developed hermaphroditic sexual apparatus admirably adapted to prolong the existence of the race by the production of enormous numbers of ova, are practically all that is left of what were at one time the complex organs of a highly developed worm. Similar adaptation by atrophy is seen in Linguatula, related to the spiders, but because of its simple tape-like structure long considered to be a worm, as shown by its now abandoned name, *Tænia rhinaria*. Even the ectoparasites show similar degenerations. The rudimentary wings of the bedbug are succeeded in the next downward phase by the wingless lice, all need for such organs having ceased long since. Finally, the ingenious mechanisms for propagation of the species by alternations of generations, passing from man through the lower animals, or in case of the *Tænia echinococcus*, from the dog through man, show the most remarkable adaptations, doubtless requiring long periods of time. Some of these have lost their original significance as in Trichinella, for in this instance, where the active parasite is the embryo and not the parent worm, the encystment in human muscle serves no useful purpose in propagating the race, the normal host of which is the sewer rat.

The effects of parasitism depend, therefore, to a certain extent upon the mutual relationship between the parasite and the host. The least perfectly adapted parasites are the ones which are apt to cause destruction of the host and thereby, so to speak, defeat their own ends. Good examples of this are some of the fatal bacterial diseases, which by destroying the life of the person in whom they develop check their own distribution to other individuals. Virulence, therefore, may be synonymous with lack of adaptation. At the other end of the scale, are found examples of what is called symbiosis, in which the parasite and the host live ami-

cably together, neither causing damage to the other. An example of this is the occurrence of the colon bacillus in the human intestine, or, in the case of ectoparasites, of some of the lice which commonly infest birds; these do not suck the blood but eat only the dried epidermal scales shed by the skin and rarely affect the health of the carrier. A similar symbiosis may occur even in exceptional individuals who are not susceptible to a highly virulent parasite; for example, the frequently noted "typhoid carriers." In such cases the typhoid bacillus does not damage the host, in whose intestinal tract it may flourish for years.

The limitations in space prevent the consideration of more than a small fraction of the animal parasites. For example, there are at least sixty nematode worms which occur in man, but only eight of these can be even mentioned. The student, therefore, is referred for details concerning the rarer parasites and technical methods to the larger works on the subject[1] which also contain much interesting biological lore.

Protozoa.

General Characters of the Protozoa.—The protozoa are, with few exceptions, unicellular animal organisms of a primitive type, reproducing by division, by budding, and by spore formation. Some are very minute, others many millimeters in diameter. Some of them seem to lie between and to link the two great divisions of living beings somewhat arbitrarily established—the animals and the plants.

While some of the protozoa are relatively simple in structure, others are extremely complex. The life cycle of some forms, also, is simple, while others, passing through sexual and asexual phases, present at different periods the greatest diversity in form and function.

Some protozoa maintain an independent existence, others are parasitic for men and animals. Among the parasitic forms are important groups which require residence in the body of more than one animal species for the completion of their life cycle. Many of the protozoa possess organs of locomotion, pseudopodia, flagella, or cilia.

Our knowledge of the protozoa parasitic in man is of recent date, but is accumulating with great rapidity especially as regards tropical forms. Many forms are so difficult to study and to classify that for the moment, in numerous instances, conjecture and a balancing of probabilities and analogies are made to do duty in lieu of facts.

Although not yet proved, it is widely believed that some, if not all, of the exanthemata, yellow fever, trachoma, molluscum contagiosum, and it may be hydrophobia, are incited by some form of parasitic protozoa belonging to the subgroup, *Chlamydozoa*.

Modes of Transmission of Protozoan Parasites.—Some forms of protozoa are transmitted by *contact*, as certain trypanosomes and the syphilis organism; others are *ingested* with food and drink.

[1] *Mense, C.*, Handbuch d. Tropenkrankheiten, 2d ed., Leipzig, 1913; *Stiles, C. W.*, New York Med. Jour., 1903, lxxviii, 877; *Brumpt*, Précis de parasitologie, 2d ed., Paris, 1913; *Neumann* and *Mayer* Wichtige tierische Parasiten und ihrer Übertrager, Munich, 1914; *Fantham, Stephens*, and *Theobald*, Animal Parasites of Man, London, 1916.

Congenital transmission of the syphilis organism is of frequent occurrence.

So confident are many observers that smallpox and scarlatina are incited by protozoan parasites, presumably by such as in the development of their life cycle form minute spores, that they venture to assume that in these diseases, at least, the infective agent may be *air-borne* in floating dust.

Finally, in many instances, infection takes place through *transmission by intermediate hosts.* This occurs in malaria and yellow fever, and with certain trypanosomes and sporozoa. In the transmission of the malarial organism by the mosquito and in the case of some trypanosomes, important phases in the life cycle of the parasite take place in the body of the intermediate host. Other insects—lice, ticks, bedbugs, and leeches—act as intermediaries.

The Effects of Protozoan Parasites upon their host are in many cases obvious, in many quite obscure. We shall consider some of these in the brief review of species which follows.

Cultivation of Protozoa.—It has been found practicable to cultivate on artificial media, through a few generations at least, some forms of protozoa—amebas, trypanosomes, and the malarial parasite; but the knowledge thus far derived from such artificial cultivation is scanty.

The scope of this book permits only a very limited consideration of the most significant forms of protozoa which are related to human pathology.[1]

I. Rhizopoda.

The protozoa of this division are usually of simple structure, characterized by motile organs in the form of pseudopodia. Reproduction is by division and by spores.

Entamœba histolytica (Amœba dysenteriæ) is of considerable pathologic importance. Councilman and Lafleur[2] in 1891 first definitely established the significance of this protozoan parasite which they called *Amœba dysenteriæ,* a name now superseded by *Entamœba histolytica* of Schaudinn.

It has been repeatedly found, most frequently in the tropics, in acute and chronic dysentery, in the intestinal contents, at the bottom of the intestinal ulcers, and in the secondary abscesses, especially of the liver, which may accompany ulcerative colitis, and is believed to be the inciting factor, in some cases, in both the primary ulcerative colitis and its complicating abscesses (see page 779).

This ameba (Fig. 78) is a spheroidal cell, from five to ten times the diameter of a red blood-cell, with granular protoplasm and a vesicular

[1] The best presentation of our present knowledge of protozoa is contained in *Doflein,* Lehrbuch d. Protozoenkunde, 3d ed., Jena, 1911, which includes an extensive and well-classified bibliography. *Calkins,* Protozoology, New York, 1910, is a readable epitome of the subject; and *Park* and *Williams,* Pathogenic Microorganisms, 8th ed., New York, 1924, contains a great deal of fundamental information on pathogenic forms. See also *Prowazek, S.,* Handbuch d. path. Protozoen, Leipzig, 1912.

[2] *Councilman* and *Lafleur,* Johns Hopkins Hosp. Rep., 1891, ii, 395.

nucleus. It often contains larger and smaller vacuoles, bacteria, and phagocyted red corpuscles. Frequently, especially when the ameba is active, a portion of the protoplasm appears almost homogeneous—ectosarc—while the rest—endosarc—is granular. When moving it assumes various forms, thrusting out and withdrawing nearly homogeneous pseudopodia. It may also change its shape without progressive movement. In chronic or convalescent cases of amebic dysentery, when the feces have become formed, there may be found, in addition to the vegetative forms, the encysted or generative stage. These are globular, yellow masses with a thick wall and from two to sixteen nuclear masses. Chromidial masses are often present, distinct from the nuclei.

The parasite occurs in acute and chronic dysentery, frequently in the United States and Egypt, and occasionally in Russia, India, Panama, and the Philippines.[1] It is capable of making its way between the epithelial cells of the gut, usually of the large intestine, and penetrating to the submucosa. There it causes necrosis of the tissues with the formation of an abscess which breaks through the mucosa and discharges into the gut lumen, thus forming the characteristic amebic ulcer with overhanging walls. Abscess of the liver is often secondary to the intestinal lesion; abscesses in the lung are not infrequent; those in the brain and spleen are very rare. Carriers are frequent,[2] possibly ten per cent. of the population. Only a small portion of such carriers have or have had characteristic dysentery; most of them suffer from amebiasis with mild digestive or neurasthenic symptoms.

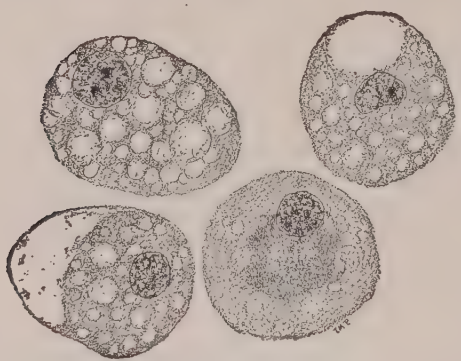


FIG. 78.—ENTAMŒBA HISTOLYTICA.
From the intestinal wall near an ulcer in amebic colitis.

The organism has been artificially cultivated.[3] Animal inoculations are easily made, especially in young cats, with the production of an acute colitis.

Other species of ameba have been found in the human mouth, intestines, and bladder, but are apparently not pathogenic. The *Entamœba coli* is very frequently present in health and in intestinal disorders other than dysenteric. The coli type is differentiated from the histolytica by the lack of distinction between ectosarc and endosarc, by the more highly refractile and central nucleus, by absence of phagocyted red cells, and by the greater frequence of large encysted forms without chromidial

[1] For full description, see *Dobell, C.*, Amebæ Living in Man, London, 1919; *Dobell, C.*, and *O'Connor, F. W.*, The Intestinal Protozoa of Man, New York, 1921.

[2] *Craig*, Jour. Am. Med. Assn., 1927, lxxxviii, 19.

[3] *Boeck* and *Drbohlav*, Am. Jour. Hyg., 1925, v, 371; *St. John*, Jour. Am. Med. Assn., 1926, lxxxvi, 1272.

masses. The type found in the mouth is supposed to be connected with peridental inflammation in the form of Riggs' disease.[1]

There is reason to believe that amebas are acquired through drinking-water and uncooked foods.

II. Mastigophora.

These organisms are of definite or changeable shape, with or without a membrane. They are characterized by the possession of one or more

Fig. 79.—Trypanosoma Brucei.
The protozoan parasite of the tsetse-fly disease of Africa. The two upper parasites show the dot-like blepharoplasts at their blunt posterior extremities.

undulating or vibratile processes or flagella. Some forms seem to be closely related to the bacteria.

Trypanosomes.—Among the flagellated protozoa the trypanosomes are of much significance, occurring as free-swimming parasites in the blood of both cold- and warm-blooded animals—mammals, birds, reptiles—and in the intestines of certain blood-sucking insects—flies, mosquitoes.

[1] *Bass, C. C.*, and *Johns, F. M.*, Alveodental Pyorrhea, Philadelphia, 1915; also Jour. Am. Med. Assn., 1915, lxiv, 553.

Trypanosomes are elongated, and usually pointed, and may have one or two flagellæ and an undulating membrane at the side attached to the flagella (Fig. 79). The membrane is often attached in folds or undulations so that the movement of the parasite in swimming is somewhat augur-like. There are two nuclei: one, large and near the center of the organism, is the trophic nucleus; the other, small and often rod-like, is situated in the posterior portion of the organism at the termination of the flagellum; this is the blepharoplast or kinetic nucleus. The flagellum forms an edge to the undulating membrane. Sometimes a small granule is situated at the origin of the flagellum; this is called the basal granule and is considered by some observers to act as the centrosome of the kinetic nucleus. The organisms divide by fission, which process is preceded by division of both nuclei. Small oval bodies without flagella may be found in the internal organs.

In many instances the trypanosomes seem to be of no special significance to the host, but in several of the lower animals and in man some species are markedly pathogenic.

Trypanosomes are common in wild rats in all countries. The species infesting these animals, *Trypanosoma lewisi*, can be readily transmitted with the blood to a fresh animal by injection and does not appear to interfere with the well-being of the rats. A certain immunity to subsequent injections seems to be conferred by the presence of these parasites in the blood of the rat, from which they usually disappear in two or three months.

Novy and McNeal first successfully cultivated the Tr. lewisi and other forms on nutrient agar containing varying amounts of defibrinated or laked rabbit blood.

Pathogenic Trypanosomes.

Tsetse-fly Disease.—Among the more important of the trypanosome infections we may note *Nagana* or the tsetse-fly disease (Fig. 79). This infectious disease of cattle, horses, and mules occurring in Africa, especially in Zululand, has long been known and was at one time of great economic importance. It is characterized by fever, emaciation, edema, etc.

In 1894 Bruce discovered a trypanosome—*Trypanosoma brucei*—in the blood of the affected animals. He also found that the parasite was conveyed to healthy animals through the bite of a tsetse-fly of that country—*Glossina morsitans*—which had shortly before bitten an infected animal. The original source of the parasite was found to be the wild animals of the region, which did not appear to be affected by it. There is still some doubt as to the differentiation of this form from *Trypanosoma gambiense* and *Trypanosoma rhodisiense*.[1]

Surra.—This disease of horses and cattle, occurring in India, and possibly in other tropical countries, has been shown to be due to a

[1] *Bruce*, Proc. Roy. Soc., Ser B., 1914, lxxxvii, 526.

trypanosome, *Trypanosoma evansi*, which is conveyed from infected to healthy animals by a fly.

Several other diseases of wild and domestic animals are known to be incited by trypanosomes.

Sleeping Sickness.—The "sleeping sickness" is very common and fatal among the negroes of equatorial Africa, assuming in the Congo region the character of a veritable pestilence whose victims number hundreds of thousands. White men are not exempt. The disease, still rapidly extending, is characterized by lethargy, debility, emaciation, drowsiness, coma, and death. The cerebral lesions resemble those of syphilis.[1] The disease is incited by a trypanosome, *Trypanosoma gambiense*, which also is conveyed by a tsetse-fly, *Glossina palpalis*. The

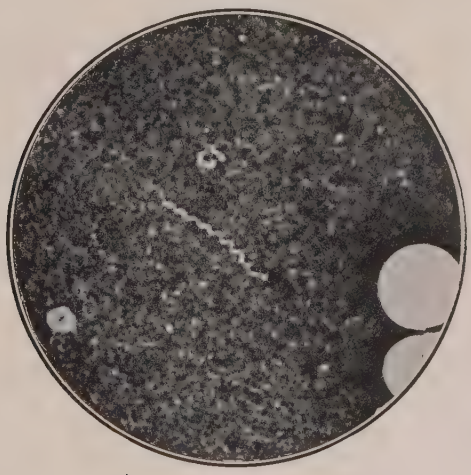


FIG. 80.—TREPONEMA PALLIDUM.
Demonstrated by the India ink-method (see p. 317).

lesions noted are congestion of the meninges with fluid exudate and enlargement of the lymph-nodes, spleen, and liver.[2]

A second form, *Trypanosoma rhodesiense*,[3] transmitted by *Glossina morsitans*, has been described as also causing an acute form of sleeping sickness, but its distinction from Trypanosoma gambiense is not yet certain.[4]

Chagas has also described *Trypanosoma cruzi* as occurring in Brazil and transmitted by the bite of an insect, *Conorhinus megistus*. This parasite causes an acute meningoencephalitis, often fatal, and also an

[1] *Spielmeyer*, Lewandowsky, Handb. d. Neurologie, Berlin, 1912, iii, 538.

[2] For a summary of trypanosomes and diseases incited by them, see *Novy, F. G.*, Jour. Am. Med. Assn., 1917, xlviii, 1; *Laveran* and *Mesnil*, Trypanosomes and Trypanosomiases, Trans. by Nabarro, Chicago, 1907, or 2d French ed., 1912. Also *Mayer, M.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, vii, 321. For a study of trypanosomiasis with special reference to service in the Philippine Islands, see *Musgrave* and *Clegg*, Bureau of Govt. Labt., Dept. of the Interior, Biol. Lab., No. 5, 1903. For a study of chemical therapy, see *Terry, B. T.*, Arch. Int. Med., 1909, iii, 98.

[3] *Stephens* and *Fantham*, Ann. Trop. Med. and Parasit., 1910, iv, 343.

[4] See, for some rather destructive criticism for using relative measurements as a basis for separating this parasite from Trypanosoma gambiense, *Pearson, K.*, Biometrika, 1914, x, part I, 85.

acute thyroiditis with swelling of the superficial nodes. If the disease passes into a chronic type it resembles cretinism, often accompanied by paralysis and cerebral defects.

Spirochæta.

Among the spirally curved bacteria it has been customary to recognize a genus called *Spirillum*, the members of which have a rigid spirally curved body, and a genus called *Spirochæta*, in which the organisms are also spirally curved but are described as flexible. These genera have been considered to embrace closely related bacterial forms.

The discovery by Schaudinn of *Spirochæta*, now called *Treponema pallidum* (Fig. 80), in the lesions of syphilis has given rise to many critical studies of spirochetes, and while we cannot enter here into the details of the matter, it has finally become probable, if not entirely proved, that the spirochetes are protozoa and not bacteria or at least that the protozoan characters are predominant in them.[1]

The fact that the synthetical chemical compound of arsenic, dioxydiamido-arsenobenzol, popularly known as salvarsan, has a specific destructive action on the life, not only of the spirochetes of syphilis and of relapsing fever, but of trypanosomes as well, would indicate a relationship between the spirochetes and the protozoa which tends to confirm the evidence from morphology.

The occurrence of spirochetes in tumors is of no pathological significance.

Treponema pallidum (*Spirochæta pallida*).—This organism, now believed to be a protozoon and the inciting agent in syphilis, is described in connection with the lesions of that disease (page 314).

A similar organism, *Treponema pertenue* (*Spirochæta pertenuis*), has been found in yaws (page 308).

Spirochæta obermeieri (*Borrelia recurrentis*) and *Borrelia duttoni*, the protozoan organisms which are the cause of relapsing fever, are described in connection with that disease (page 330).

In a disease known as rat-bite fever,[2] there has been found a spirochete, called Leptospira or *Spirochæta morsus muris*. The organism is thicker than the Treponema pallidum, and usually has from 1.5 to 6 bends at intervals of about 1 micron, with flagella at both ends. It is gram-negative, but stains easily with aniline dyes and silver, and can be demonstrated in the blood, skin, and lymph-nodes of persons suffering from the disease. It is present in about 3 per cent. of house rats and infects also white rats, mice, and monkeys.

In a case of a similar disease following a rat bite, the *Streptothrix muris ratti* of Schottmüller has been isolated;[3] so that it appears probable that more than one organism can induce the uncharacteristic group of symptoms observed after rat bites.

[1] For a discussion of this subject, see *Calkins*, Protozoology, New York, 1910, p. 231; also *Arnheim*, Ztschr. f. Hyg., 1914, lxxvi, 407.

[2] *Futaki, Takaki, Taniguchi*, and *Osumi*, Jour. Exper. Med., 1916, xxiii, 249; 1917, xxv, 33 (bibl.).

[3] *Schottmüller, H.*, Dermat. Wchnschr., 1914, lviii, Suppl. 77; *Blake, F. G.*, Jour. Exper. Med., 1916, xxiii, 39 (bibl.).

Another spirochete, *Spirochæta icterohæmorrhagiæ*, is considered as causing the type of acute infectious jaundice known as Weil's disease.[1] This organism is found in wild rats, and measures from 3 to 4 or even 40 micra, with about two coils to the micron. It is a facultative anaerobe, growing fairly well on ascitic fluid to which has been added a piece of sterile kidney,[2] a method generally useful for the spirochete.[3] Similar organisms have been found in persons suffering from acute jaundice in Japan, France, Belgium, and America. There are no characteristic lesions, though the liver may be the site of a catarrhal cholangitis or even of an extreme alteration resembling yellow atrophy. The kidney shows parenchymatous changes or a considerable tubular nephritis and contains large numbers of spirochetes which are, in consequence, abundant in the urine. They are not abundant in the spleen or lymph-nodes, though both are enlarged. The disease is not often fatal.

A large number of cases of obscure infections, some with and others without jaundice, have been seen among the soldiers in the trenches during the present war. Spirochetes are usually abundant in the urine in these cases, and in many instances have been identified as *Spirochæta icterohæmorrhagiæ*.[4] Whether spirochetes of other species act as infectious agents in some of the fevers without jaundice has not yet been determined.

Leishmania.—There are three diseases due to parasites of this genus, which is more closely allied to the genus Herpetomonas than to Trypanosoma.

Leishmania donovani[5] is the inciting agent of Indian kala-azar or dum-dum fever, a disease characterized by fever, emaciation, splenic tumor, anemia, and leucopenia. It occurs at all ages and is usually fatal. Cases have been observed in India, China, Syria, and the Soudan. The organism is rarely found in the blood, but is very abundant in the splenic pulp and in the endothelial cells of the capillaries of other organs. It does not invade the red cells, but is frequently phagocyted by the leucocytes. It is a small oval organism, measuring 2 by 3 microns, and having the nucleus and blepharoplast of the flagellates. It can be cultivated in artificial media. The extra-human host and transmitter of the disease is probably the bedbug.

Leishmania tropica[6] produces a disease known as Delhi boil, an indolent ulcerative lesion often confined to the exposed portions of the body. The disease is self-limited and immunity follows. The parasite is abundant in the tissues about the ulcerated area and in morphology resembles Leishmania donovani. It is infrequent in the blood. The disease occurs in India, Arabia, and the Mediterranean littoral. A very similar type, called uta, is found in South America.[7]

Leishmania infantum[8] causes a disease in children and dogs resembling

[1] *Inada, Ido, Hoki, Kaneko,* and *Ito,* Jour. Exper. Med., 1916, xxiii, 377; *Noguchi, H.,* Jour. Exper. *Med.,* 1917, xxv, 755 (bibl.).
[2] *Ito* and *Matsuzaki,* Jour. Exper. Med., 1916, xxiii, 557.
[3] *Noguchi, H.,* Jour. Exper. Med., 1912, xvi, 199; *Knoepfelmacher,* Ergebn. d. inn. Med., 1910, v, 205.
[4] *Dawson, Hume,* and *Bedson,* Brit. Med. Jour., 1917, ii, 345 (bibl.).
[5] *Leishman,* Brit. Med. Jour., 1903, i, 1252; and *Donovan, C.,* ibid., 1903, ii, 79; Lancet, 1904, ii, 744.
[6] *Wright, J. H.,* Jour. Med. Research, 1903–04, N. S. v, 472.
[7] *Strong, R. P.,* and others, Jour. Am. Med. Assn., 1913, lxi, 1713.
[8] *Nicolle,* Arch. Inst. Pasteur de Tunis, 1908, i, 26.

kala-azar and characterized by fever, anemia, leucopenia, enlargement of the spleen and liver, edema, and subcutaneous and submucous hemorrhages. It is generally fatal. The parasites are rare in the blood, but can be easily demonstrated in fluid from splenic puncture. The disease is most frequent along the Mediterranean littoral. The parasite resembles Leishmania donovani in morphology, and differs from it but little in its biological characters. The dog flea is supposed to transmit it.

All these species can be cultivated on artificial media.[1]

Fig. 81.—Trichomonas Vaginalis. After Dock.

Trichomonas vaginalis has an oval or pear-shaped body from 0.015 to 0.025 mm. long, with a cluster of flagella at one end and an undulating membrane, frequently mistaken for cilia, upon the side (Fig. 81). It is of occasional occurrence in vaginal exudates. The possibility of mistaking the organism for human spermatozoa should be borne in mind in medicolegal examinations, although to an observer familiar with either structure such a mistake could hardly occur.

Some forms of Trichomonas have been found in the urine of man, in the intestines, and in the sputum.[2]

Lamblia intestinalis is a pear-shaped flagellate with eight flagella, which is found in its vegetative form in the small intestine, but more usually encysted in formed feces. It is thought to be responsible for certain tropical diarrheas, in which condition the flagellate forms are found in the fluid stools.

Cercomonas hominis, an oval parasite, 10 to 12 micra long, with a single flagellum, has been found in diarrheic stools. It is related to trypanosoma. In all probability no one of these flagellates is very pathogenic for man.

III. Ciliata (Infusoria).

The infusoria are the most highly differentiated of the protozoa. They have numerous motor appendages or cilia, which may persist through life or in some forms be replaced in the adult stage by suctoria. They reproduce chiefly by fission or budding. Among the ciliated infusoria, few if any are pathogenic in man. The *Balantidium coli* (Fig. 82) is an ovoidal organism from 0.06 to 0.1 mm. long; it is a common parasite of swine in some regions, and has been found in the intestinal tract of man under conditions which indicated its pathogenic significance as the inciting agent in the causation of acute and chronic dysentery, often with ulceration of the bowel.

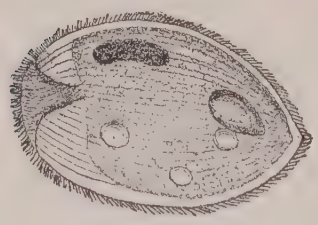


Fig. 82.—Balantidium Coli. After Braun.

The parasite is not infrequently present in the stools of inhabitants of Northern Europe, China, the Philippines, and North and South America.[3]

[1] For full details concerning leishmaniases, see *Laveran*, Les leishmanioses, Paris, 1917. For details of anemia caused by these parasites, see page 549.

[2] For original studies of Trichomonas with historical summary and bibliography, see *Dock, G.*, Am. Jour. Med. Sc., 1896, cxi, 1. See also *Lynch, K. M.*, Jour. Parasitol., 1916, iii, 28.

[3] *Walker*, Philippine Jour. Sc., 1913, Sec. B, viii, 333; *Behrenroth*, Ztschr. f. klin. Med., 1903, xix, 321; *Strong* and *Musgrave*, Bull. Johns Hopkins Hosp., 1901, xii, 31; *Askanazy*, Verhandl. d. deutsch. path. Gesellsch., 1903, v, 224; and *De Buyc, L. R.*, Am. Jour. Dis. Child., 1918, xvi, 123.

Chlamydozoa.—This name was proposed in 1907 by Prowazek for a group of hypothetical parasites supposed to be the inciting agents of hydrophobia (page 333), vaccinia and variola (page 343), trachoma (page 346), and measles (page 348), all of which belong to the class of diseases thought to be due to filterable viruses. The organisms are parasites of epiblastic tissues; that is, they are found only in cells of epidermal, conjunctival, and nerve tissue. While at one time thought to be merely cell-inclusions or degeneration products, these bodies are now believed to be true parasitic organisms. Some of them have, in fact, been cultivated.[1]

The parasites will be discussed in connection with the specific lesions of the diseases enumerated above.

Molluscum Contagiosum.—This is an epithelial hyperplasia with characteristic morphology, which is due, according to some authors[2] to an organism belonging in the group of Chlamydozoa. The virus is probably a filterable one, as the organism described is very minute. The disease is unquestionably infectious, and occurs in epidemics; the period of incubation varies from fourteen days to four months. The lesions consist of small elevated nodules of thickened epithelium containing the characteristic molluscum bodies,[3] which are, in all probability, altered and degenerated epithelial cells. There is usually a small opening on the surface of the skin through which a cheesy material containing a large number of these cells can be squeezed.

IV. Sporozoa.

The sporozoa are all parasitic, living at some period of their life cycle in the cells of their host, and are especially characterized by their reproduction through encystment and spore formation and absence of definite motile organs. Many forms of the organisms, especially the spores, are very minute and difficult of identification.

The sporozoa are widely distributed, being found as parasites in nearly all classes of animals. They may invade the gastrointestinal canal and the kidney and their adnexa, the blood, muscle, connective tissue, and skin. While many of them appear to be harmless to their host, others may do serious damage by blocking the tissue spaces and thus, or in other ways, inducing necrosis, atrophy, or cell death. Some forms are wholly intracellular, others remain for only a part of their life cycle within single forms of cells, passing then to other cells or to the body cavities or to hosts of a different species. The life cycle of many forms is extremely complex. On account of their strict parasitism and the requirements in some instances of an interchange of hosts, precluding the methods of culture applicable to many of the lower organisms, the life history of many forms is still unknown or obscure.

The classification of the Sporozoa is still tentative, but one may conveniently recognize the following orders:

[1] *Noguchi* and *Cohen*, Jour. Exper. Med., 1913, xviii, 314.

[2] *Lipschutz*, Prowazek, Handbuch d. path. Protozoen, 1912, i, 219; *Wile, U. J.*, and *Kingery, L. B.*, Jour. Cutan. Dis., 1919, xxxvii, 431.

[3] *Kromayer, E.*, Virchows Arch., 1893, cxxxii, 62.

1. *Gregarinida.*—These are round or elongated parasites, some of the higher forms presenting partitions in the cell with special development of one end for attachment. They are parasitic in certain cold-blooded animals, especially the invertebrates. The young stages only are intracellular, mature forms occurring in the body spaces.

2. The *Myxosporidia* are parasitic in certain of the invertebrates, in fishes and batrachians. Epidemics among silk worms incited by a parasite of this class have occasioned serious losses. Many species are concerned in diseases of fish, in which they may cause extensive deep foci of necrosis and ulceration.

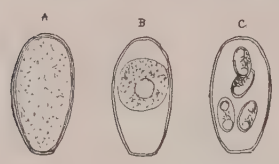


Fig. 83.—Coccidium Oviforme.
This shows the encapsulated form of the parasite, with the formation of spores.

3. *Coccidiidea.*—Organisms of this order are parasitic in certain of the invertebrates, in birds, reptiles, and mammals. They are round or oval, usually intracellular parasites having no free motile adult stage. They are most frequently found in the epithelium of the intestine and liver. One of the most common forms in the mammalia is *Coccidium oviforme* (*Eimeria stiedæ*) (Fig. 83) which is of frequent occurrence in the intestine and liver of the rabbit, forming a part of the contents of yellowish, irregular shaped masses, resembling tumors, or in the form of cysts.[1]

The parasites surround themselves with a capsule within which elongated sporozoites develop. This encapsulated form may be taken up by a new host in which the sporozoites are set free and enter the epithelial cells in which they again become encapsulated. The occurrence of *Coccidium oviforme* has been recorded in the liver, kidney, intestine, and heart-muscle of man.

Another smaller form, occurring in the intestinal epithelium of dogs, cats, and rabbits, has been found in two cases in a similar situation in man.

Fig. 84.—Sarcocystis Muris.

4. *Sarcosporidia.*—In this order of the Sporozoa the usually elongated slender early stage is found in between the muscle fibers and bundles of vertebrates—mouse, hog, and, in a few instances, in man. These are commonly known as the "tubes of Miescher" or "of Rainey" (Fig. 84). Reniform or falciform spores are developed. The adult forms are spheroidal or elongated. The life cycle is not well known.[2]

[1] See *Tyzzer, E. E.*, Jour. Med. Research, 1902, N. S. ii, 235.

[2] For a study of the production of sarcosporidia in the mouse, see *Smith, Th.*, Tr. Assn. Am. Phys., 1901, xvi, 576.

5. *Hæmosporidia.*—These parasites of the blood form a large group occurring in the corpuscles or plasma of vertebrates—amphibia, reptiles,[1] birds, and mammals. Some forms are among the most important of the protozoan parasites of man. They are of small size; the adult form is motile. One stage in the life cycle is passed in the blood of the vertebrate host; another in the body of some insect, as an intermediate host.

Among the mammalian hemosporidia we may mention the hematozoon of malaria and the hematozoon of Texas fever.

Malaria.—The characters of the malarial hematozoon, for which the mosquito acts as intermediate host, are described in detail on page 344.

Texas Fever.—Texas fever (tick fever), a disease of cattle marked by fever, debility, and hemoglobinuria, occurs in many parts of the world—North and South America, Europe, and Africa. The hematozoon inducing Texas fever was discovered by Theobald Smith and Kilbourne[2] and is now called *Babesia bigemina.* In one stage it is a minute pyriform organism occurring often in pairs in the red blood-cells of its host. Free forms have been found in the blood. While its life cycle has not been completely worked out, Smith and Kilbourne showed that a cattle tick acting as an intermediate host transmits the parasite through her eggs and larvæ. It is through these young ticks that fresh cattle become infected.[3] Other species of Babesia have been found in the dog in various countries; still others in horses and sheep.

Methods of Study of the Protozoa.

The protozoa may be studied in the living condition in the fluids in which they are found or they may be killed by a saturated sublimate solution and stained with iron hematoxylin.

The movements of the Entamœba histolytica in the feces or in the contents of abscesses, may be studied on the warm stage. Its morphology may be studied in tissue containing it, such as intestinal ulcers, abscesses, etc., which have been hardened and stained with either methylene blue or iron hematoxylin.

The attempts to obtain pure cultures of certain forms of ameba and similar or allied forms of protozoa have been partially successful. The method by which McNeal and Novy obtained pure culture of trypanosomes, namely, by the use of ordinary nutrient agar containing rabbit's blood, is of high promise in related forms of protozoa.[4]

Metazoa.

Among the multicellular parasites, the worms—the flat flukes and tapeworms as well as the round worms and a few insects—form the most important classes for our consideration. But for the details concerning these as well as the other larger parasites we must refer to special works on parasitology.

It may be said in general that the metazoan parasites may be harmful to the structure or the function of the host, though the damage is

[1] For discussion of hemosporidia in American reptiles and batrachians, see *Langmann*, New York Med. Jour., 1899, lxix, 1.

[2] *Smith*, Bureau of Animal Industry, Bull. No. 1, 1893.

[3] For a summary of observations on Texas fever (hemoglobinuria of cattle) see *Schilling, C.*, and *Meyer, K. F.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, vi, 481.

[4] For details of this method as well as a résumé of the cultivation of protozoa, consult *McNeal* and *Novy*, Contributions to Medical Research, Vaughan Anniversary Volume, 1903, p. 549.

often very slight, either by their local presence, occluding canals, obstructing vessels, inducing local irritation, or structural damage; or by their movements about the body; or by the appropriation of food belonging to the host; or finally, by the setting free of deleterious metabolic products of their own manufacture.

This toxic action of certain parasites is especially marked by the more or less pronounced eosinophilia present in a large proportion of patients who are the victims of invasion by parasitic worms.[1]

The frequent anemia associated with the presence of metazoan parasites and the local injuries inflicted by them, especially on the mucous membranes, through which the body is made more vulnerable to secondary bacterial invasion, are all of considerable importance. Some of these effects will be referred to in the following brief series of individual forms of metazoan parasites.

Worms.

TREMATODA (Flukes).

These worms are small, flat, tongue-shaped, or leaf-like creatures, with an intestine and a discoidal structure on the under surface, by means of which they attach themselves. There are several genera and species found in man. Of these, *Fasciola hepatica* (*Distomum hepaticum, liver fluke*) is a frequent and usually fatal parasite of sheep (Fig. 85); about 28 cases of infection in man have been observed, usually without symptoms, though in severe cases enlargement of the liver and

Fig. 85.—Fasciola Hepatica.
About natural size.

jaundice have been noted. *Fasciolopsis buski* (*Distomum buski*) is a larger parasite, measuring 70 mm. as a maximum. Its normal site is the intestine of the pig; but it occurs frequently in the intestine of man in India, Siam, and China. *Paragonimus ringeri* (*Distoma pulmonale*) and its related form *Paragonimus westermanni* are frequently found in the lungs, pleuræ, and bronchi of the Chinese and Japanese, inciting serious acute and chronic inflammatory lesions. The eggs are found in the sputum.

Opisthorchis felineus (*Distoma lanceolatum*) is a small parasite, 8 to 11 mm. in length, and 1.5 to 2 mm. in diameter, which normally inhabits the gall-bladder and bile-ducts of the domestic cat. In some places in Siberia it is the most frequent parasite of man, occurring in some 6 per cent. of autopsies. Elsewhere the parasite is extremely rare.

Clonorchis sinensis (*Distoma siense*) is a parasite of local distribution in certain parts of China. In man the parasite is found in the bile-ducts.

[1] See, for a study of the influence of parasites on the host, *Ward*, Science, 1907, xxv, 201; consult also *Shipley* and *Fearnsides*, Economic Biol. Jour., 1906, i, 41.

Schistosoma hæmatobium (*Distoma hæmatobium, Bilharzia hæmatobia*) is a cylindrical worm with distinct sexes. The female, which measures about 20 mm. in length and 0.25 mm. in diameter, is clasped in a long groove on the ventral surface of the male, which measures 12 to 14 mm. long and about 0.5 mm. in diameter. The parasites occur in the veins of the portal system. The eggs, which are responsible for many of the pathological conditions induced by the parasites, are ovoid, chiefly with terminal spines, and are found abundantly in the liver and in the stools and urine. Serious inflammatory lesions of the bladder and rectum

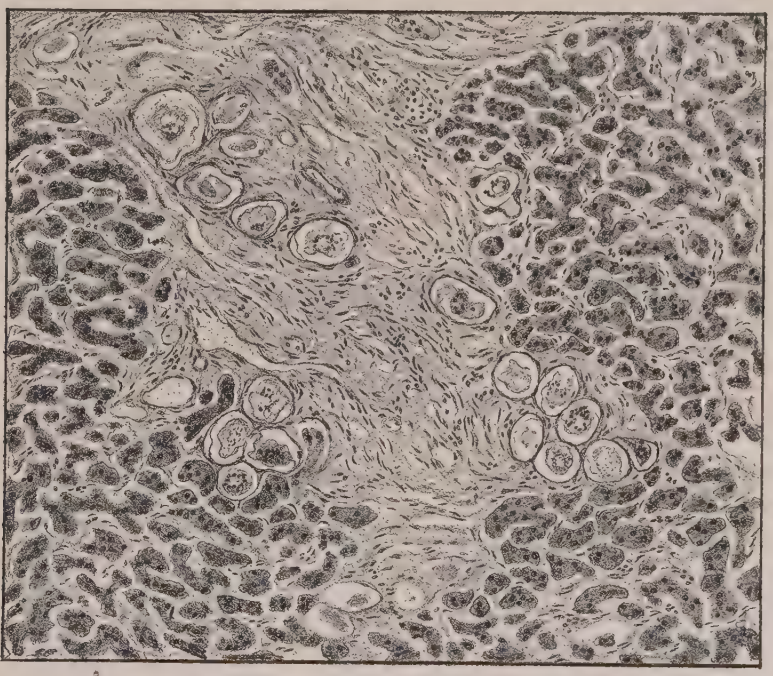


FIG. 86.—SCHISTOSOMA JAPONICUM IN THE LIVER.

are frequently caused by the irritation of the eggs, and may result in the production of carcinoma in these regions. The parasites are widely distributed in Africa and are especially frequent in Egypt.[1] Another species, *Schistosoma mansoni*, occurring in the Congo, the West Indies, and Brazil, differs slightly from the previous parasite, and is thought to form eggs with lateral spines only. *Schistosoma japonicum* is a parasite differing but slightly from those just described and occurring in Japan, China, and the Philippines. It is found in domestic animals and in man. The lesions are chiefly of the intestine and liver, the bladder remaining free. The presence of the parasite in the liver may incite extensive cirrhosis due to the irritation (Fig. 86).

[1] For description of parasite and report of case seen in New York, see *Short, J. J.*, Jour. Amer. Med. Assn., 1919, lxxii, 630.

CESTODA (Tapeworms).

These important worms consist, in the mature state, of more or less rectangular or elongated flat segments, each one representing a single individual, arranged in a linear series to form a colony. At one end of this, called the head, is a variously formed structure for the attachment of the colony to its host. The neck and head are called the *scolex*, while the segments are called *proglottides*. These worms have neither mouth nor alimentary canal. They are hermaphrodites, the sexes being united in the proglottides. The head and neck (scolex) may exist as an immature form in various tissues and organs where they are encysted, and are often called cysticercus.

Fig. 87.—Head of Tænia Solium.
× about 40.

Tænia solium is of infrequent occurrence in man. It may be several meters in length, and may be coiled up or stretched out in the small intestines. Several worms may be in the gut at one time. The head, about the size of a pin's head (Fig. 87), has a projecting proboscis or rostellum, around which is arranged a double row of horny hooklets. Below these are four sucking discs at the sides of the head. The hooklets of the anterior row are larger than those in the posterior row, and are from 0.16 to 0.18 mm. long. The proglottides, when fully developed, are from 10 to 12 mm. long and from 5 to 6 mm. wide, but those nearest the head are much shorter and immature. The eggs of Tænia solium are ovoidal structures, about 0.03 mm. in diameter. The embryo of this worm is most commonly seen in the muscles of the pig as an encysted scolex, commonly called a "measle." It occasionally occurs in man in the muscles, brain, eye, etc., and is called *Cysticercus cellulosæ*. It is usually about the size of a pea, but may be as large as a pigeon's egg, and is surrounded by a connective-tissue capsule.

Fig. 88.—Tænia Saginata. Head and Proglottides.

A, head × about 15. *B*, mature proglottid, showing generative apparatus. *C*, head and fragments of immature proglottides, showing gradual tapering of the neck. Natural size.

Infection with the worm occurs in the human subject from the inges-

tion of insufficiently cooked "measly" pork, or, in the case of Cysticercus cellulosæ, from the ingestion of the eggs, which may, in a variety of ways in uncleanly persons, get into the food.

Tænia saginata (*Tænia mediocanellata* LEUCKART).—The head of this species is somewhat cuboidal, with neither rostellum nor hooklets, but with four sucking discs (Fig. 88). The segments are generally broader and shorter than in Tænia solium, and the worm is usually larger. In the embryonal form the scolex occurs as the *Cysticercus tæniæ mediocanellatæ* in the form of small cysts in the muscles of cattle, from the eating of which in the uncooked condition the infection occurs. This is the most common tapeworm in the United States.

Tænia echinococcus.—This worm in the mature condition forms a short, small colony inhabiting the intestine of the dog. The head is about 0.3 mm. in diameter and has a double row of hooklets around the rostellum. The proglottides are three or four in number, the last being the larger. The entire colony is not more than 4 to 5 mm. in length. The significance of this parasite in human pathology depends upon the cysts, called *hydatids*, which it forms, in the immature or cysticercus stage, in various parts of the body. Intimate association with dogs favors the acquirement of this parasite. When the eggs of the mature worm get into the intestinal canal of man they undergo partial development and find their way into the tissues and organs, most frequently into the liver. Here cysts are formed which become encapsulated by a connective-tissue membrane produced by the inflammatory reaction of the organ.

The cyst wall of the parasite is formed of two layers—an outer, finely lamellated layer called the *cuticula* (Fig. 89), and an inner, granular layer containing muscle fibers and blood-vessels, called the *parenchymatous layer*. Inside of the primary cyst, secondary cysts sometimes form, called *daughter cysts;* and within the latter, tertiary cysts, called *granddaughter cysts*, may develop. On the inner surface of the cysts, either primary, secondary, or tertiary, the scolices or heads of the immature worm are formed. These develop in the walls of the pediculated vesicles called *brood capsules*. The walls of these vesicles have a lamellated cuticula and a parenchymatous layer similar to those of the primary cysts. The scolices, of which there may be several in each brood capsule, are similar to the heads of the mature tapeworm. They are about 0.3 mm. in diameter, having a rostellum surrounded by a double row of hooklets and four sucking discs (Fig. 90). At the posterior end of the scolex is a pedicle by which it is originally attached to the wall of the brood capsule. Little, lamellated concretions of lime salts are often present in the scolex. The anterior portion of the scolex, the rostellum,

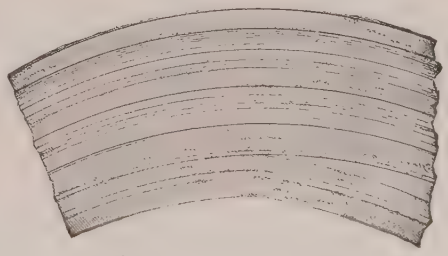


FIG. 89.—CUTICULA OF ECHINOCOCCUS CYST. Showing lamellated structure.

hooklets, and suckers, are often invaginated in the posterior portion. The scolices may be free inside of the brood capsules, or, owing to the rupture of the latter, they may be free in the cavity of the primary cysts. They may die and degenerate, forming a granular mass in which the hooklets may be embedded, or the hooklets may be free in the brood capsules or in the primary cysts. Sterile cysts are often found, that is, those in which neither brood capsules nor scolices are developed.

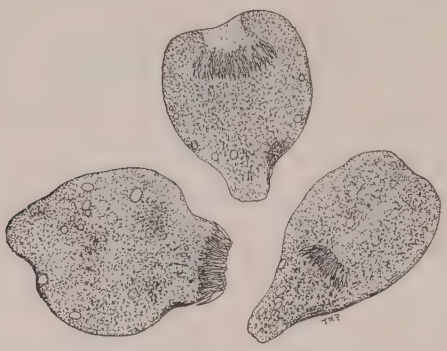


Fig. 90.—Scolices of Tænia Echinococcus. In one the rostellum is projected; in the others it is withdrawn.

The cysts contain, in addition to the scolices, a clear, gelatinous fluid. This fluid may become turbid by admixture with disintegrated scolices or fragments of the parenchymatous layer, or it may contain fatty detritus, cholesterin crystals, and particles of lime salts. The fluid may be partially absorbed, leaving a thick, grumous material within the cysts, which may become calcified or converted into a stony mass. When the scolices are not found entire the diagnosis may be made by the discovery of the separate hooklets (Fig. 91) or fragments of the characteristically lamellated cyst walls. The connective-tissue walls of the primary cysts may become fatty, or caseous, or calcified.

Sometimes the secondary vesicles project outward instead of inward, forming a series of cysts outside of the primary one. This variety of development is sometimes seen in man, but is more common in the domestic animals. It is called *Echinococcus scoleciparíens* or *exogena*.

Another variety of echinococcus, called *Echinococcus multilocularis*, is almost always found in the liver, and appears to be the result of incomplete and disturbed development of the embryos or cysts. It consists of a congeries of irregular, usually small cysts (Fig. 550, p. 852), surrounded by broad and narrow bands of connective tissue, and sometimes containing gelatinous fluid and scolices or hooklets; but the latter structures are commonly absent or difficult of detection. The whole is often surrounded by a dense connective-tissue capsule which may be calcified. The entire mass often presents an alveolar structure and was formerly regarded as a tumor—alveolar cancer. The diagnosis may be established by the discovery of the hooklets or scolices, or fragments of the lamellated cuticula. It is possible also to obtain complement fixa-

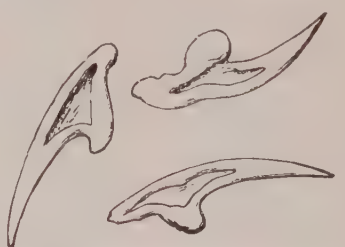


Fig. 91.—Hooklets from Scolex of Tænia Echinococcus.

tion in the blood in echinococcus disease, using the wall of the cyst as antigen. This form of the parasite is rare in America.

There are several other species of tapeworm occurring in man.

Hymenolepis nana (*Tænia nana*).—This species occurs in the form of small colonies, about 10 to 45 mm. in length. The rostellum is surrounded by a single row of hooklets. It is frequently found in the intestinal contents of Italian children, of the inmates of asylums for the insane, and of a considerable portion of the population of some of the Southern States.[1] *Hymenolepis diminuta* (*Tænia flavopunctata*), a species about which little is known, has been reported five times in America as occurring in the intestine of young children.

Dipylidium caninum (*Tænia cucumerina*).—This species occurs in colonies about 20 cm. long. The head is very small and spheroidal and has four rows of hooklets. It is frequent in the small intestine in dogs and cats, and occurs occasionally in man. Its scolex inhabits the dog louse or flea, and infection may occur by the transference of the lice or the embryos of the parasite to the mouth, as the result of the filthy habit of kissing dogs and cats or permitting the face to be licked by them.[2]

Bothriocephalus latus.—This, the largest of the human tapeworms, has very broad, quadrangular proglottides. The head is ovoidal and about 2 mm. long and 1 mm. broad. It has no proper sucking discs and no hooklets, but by long grooves on either side of the head the animal attaches itself to its host. The neck is long and filiform. It occurs most frequently in Europe, particularly in the northern provinces, though a few cases have been reported from Norwegian settlers in Minnesota. The eggs undergo partial development in water, and the larvæ are eaten by the *Cyclops strenuus* and *Diaptomus gracilis*;[3] these are then taken up by the pike and eel-pout, and perhaps by other fresh-water fish, from the ingestion of whose flesh in an imperfectly cooked condition human infection occurs. The especial importance of this parasite lies in the severe, often fatal, anemia which occasionally accompanies its presence in the intestine. Two other species of Bothriocephalus have been described as of rare occurrence in man: *Bothriocephalus cordatus* in Greenland and Iceland and *Bothriocephalus cristatus*.

NEMATODA (Round Worms).

These worms are in general cylindrical, elongated, usually pointed at the ends, and sometimes filiform. The surface is sometimes smooth, sometimes irregularly beset with hairs and papillæ, or possesses longitudinal elevated striæ or transverse rings; but the body is not segmented. There is a mouth at the anterior portion, and a ventral anus near the posterior end. The intestine is straight. The sexes are in most forms distinct, the male being in general smaller than the female.

[1] *Ransom, B. H.*, Tapeworms of the Genus *Hymenolepis* parasitic in man, Bull. 18, Hyg. Lab., U. S. P. H. S., 1904; *Stiles* and *Garrison*, Prevalence of intestinal worms in man, Bull. 28, U. S. P. H. S., 1906. For a study of the occurrence of the worm in children, see *Schloss, O. M.*, Arch. Pediat., 1910, xxvii, 100.

[2] *Blanchard*, Arch. d. Parasitologie, 1907, xi, 439.

[3] *Janicki* and *Rosen*, Cor.-Bl. f. schweiz. Aerzte, 1917, lxvii, 1505.

Ascaris lumbricoides.—This is one of the most common of the human intestinal parasites, and is of particularly frequent occurrence in children.[1] It is of a light-brownish or reddish color. The female is from 30 to 40 cm. long and from 5 to 6 mm. thick. The male is somewhat more than half as large (Fig. 92). Both sexes are pointed at the ends, the posterior end of the male being curved into a spined hook. The eggs, from 0.05 to 0.06 mm. in diameter, are surrounded by an albuminous

FIG. 92.—ASCARIS LUMBRICOIDES. About half natural size.
A, Male. *B*, Female. After Perls.

envelope (Fig. 93, A) and are quite resistant to destructive agencies. The ova when laid are not developed, so that autoinfection, common with oxyuris, is not possible. After thirty to forty days in water or moist soil, the ova reach full development, and are then transported to the human host by the ingestion of contaminated vegetables. Their usual seat in man is the small intestine, but they may wander into the stomach, and exceptionally get into the mouth, nose, bronchi, lungs,[2] gall-passages, peritoneal cavity, etc. They may be single in the gut or present in great numbers, as many as 1000 worms having been found in one individual. Such masses of worms may cause intestinal obstruction; and in addition a very irritating substance is given off by the worm, which causes intestinal disturbances. Eosinophilia is frequent.[3]

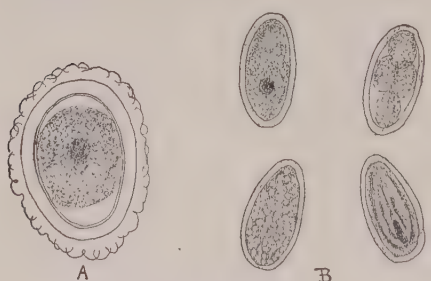


FIG. 93.—EGGS OF NEMATODE WORMS.
A, Eggs of Ascaris lumbricoides, × about 300.
B, eggs of Oxyuris vermicularis, × about 250.

Oxyuris vermicularis (Threadworm or Pinworm).—This species is very small; the female has a pointed tail and is about 1 cm. long. The posterior end of the male, which is about 4 mm. long, is blunt, and after death somewhat curled (Fig. 94). The eggs (Fig. 93, B) are produced in great numbers, are ellipsoidal, and about 0.052 mm. long. This parasite is very common in children, and may be present in large numbers in the small intestine and cecum, and less frequently in the colon. The worm is known to infest only the human subject, and infection and also autoinfection doubtless occur by the ingestion of the eggs, which are widely distributed in a variety of ways on many objects, fruits, etc. The worm may also migrate to the

[1] For a study of the frequency of occurrence of intestinal parasites in children and the clinical symptoms, see *Schloss, O. M.*, Am. Jour. Med. Sc., 1910, cxxxix, 675, and *McLean, S.*, Jour. Amer. Med. Assn., 1920, lxxiv, 1774.

[2] *Ransom, B. H.*, Jour. Amer. Med. Assn., 1919, lxxiii, 1210.

[3] *Herrick*, Arch. Int. Med., 1913, xi, 165.

nasal passages or through the vagina to the uterus and tubes, where the eggs may be deposited. If they escape from the tube, they may become encysted in hard masses of inflammatory exudate in Douglas's pouch. Local irritation about the anus is caused by the parasites which crawl out of the gut to deposit their ova. The worm is frequently found in the appendix and may cause lesions of the mucous membrane, but that it is an important agent in the incitement of acute lesions is doubtful. It does, however, frequently give rise to appendical colic by its penetration of the mucosa.[1]

A. B.

FIG. 94.—OXYURIS VERMICULARIS.
A, Female. *B*, Male.

Eustrongylus visceralis (*Strongylus gigas*).—This is a slender red worm, the female being sometimes 1 meter long and over 1 cm. in diameter. There are nine authentic records of its occurrence in the pelvis of the kidney in man. It is more common in the wolf, fox, horse, seal, and some other animals.

Uncinaria (*Hookworm*).—There are two forms of hookworm widely distributed throughout the world: one, the type originally described from Europe, the *Uncinaria duodenalis* (*Anchylostoma duodenale*); the other, the variety first described by Stiles[2] from the United States, *Uncinaria americana* (*Necator americanus*).

In the Anchylostoma duodenale, the male, which can be recognized by a large caudal bursa, is 8 to 11 mm. long, and 0.45 mm. thick, while the female, which terminates in a fine spine, is 10 to 18 mm. long, and 0.6 mm. thick. The worms are pale pink in color, often with an intense reddish tone in the posterior third; if there is much blood pigment in the cells of the intestine, the parasites may be dark. The mouth is furnished on the dorsal wall with four teeth, the ventral wall having two teeth in addition. The adult worms live in the jejunum, less frequently in the duodenum. They feed on the mucous membrane of the gut, and, as a rule, contain no blood unless a small vessel of the submucosa has been injured, in which case the parasite may be found filled with blood. The eggs are ellipsoidal, with a clear shell, measuring 56 to 61 by 34 to 38 micra. When found fresh in the feces they usually contain two to four blastomeres. The larval stage is found only after the feces have been kept for some time.[3]

In the Necator americanus, the male is 8 mm. long, and the female 9 to 11 mm. The head is sharply bent dorsally, which distinguishes the worm from the Anchylostoma duodenale. The buccal cavity is smaller than in the anchylostoma and there are no visible teeth. The spicules of the male are hooked at the extremity. The eggs are more pointed at the poles than those of the anchylostoma, measuring 64 to 72 by 36 micra. In fresh feces the segmentation is apt to be more complete, and not infrequently the larval worm may be seen inside the shell, or even free in

[1] *Cecil* and *Bulkley*, Jour. Exper. Med., 1912, xv, 225; *Aschoff*, Berl. klin. Wchnschr., 1914, li, 1504; *Suzuki, K.*, Surg., Gynec., and Obst., 1915, xxi, 702.

[2] *Stiles, C. W.*, Am. Med., 1902, iii, 777; Prevalence and Geographic Distribution of Hookworm Disease, Bull. 10, Hyg. Lab., U. S. P. H. S., 1903.

[3] For details of the development and morphology of the various stages, see *Brumpt*, Précis de parasitologie, 2d ed , Paris, 1913.

the feces. It has a slow motility, which serves to differentiate it from the similar larval form of Strongyloides stercoralis.

The anchylostoma is found in Africa, Egypt, Europe, Japan, and China, and in association with the necator is seen in India, in the southern part of the United States, and in South America. The Necator americanus is widespread, involving the people of the southern part of the United States and the adjacent islands, where it is of great importance and is the cause of extreme anemia, hemorrhage, gastroenteritis, and general debility. It is estimated that in some districts 90 per cent. of the inhabitants are affected. As the worm was undoubtedly imported by the negro slaves brought from Africa, the recent demonstration of its presence there is not astonishing; in the same fashion it has been spread in South America. In the Philippines both types are found. The reverse migration is also taking place, for Southern Europe is becoming infested with Necator americanus imported by emigrants returning from Brazil.

After the feces have been passed, the eggs develop in moist soil, and infection takes place either through water or contaminated food, by dust, especially in coal mines, or, by far the most frequent method, by infection through the skin. The mature larvæ when in contact with the skin cast their shells and rapidly bore their way through the superficial scales of the epidermis or enter the hair follicles; they then pass to the lymphatics or to the blood-vessels. By the first channel they reach the lymph-nodes, where many are retained and perish; afterwards they enter the blood-stream. If they enter a blood-vessel directly, they travel to the lungs, where leaving the stream, they enter the small bronchi, from which they travel into the trachea and larynx and thence to the esophagus and stomach. Ova can be found in the feces seven to ten weeks after the penetration of the skin. This skin transmission gives rise to what is known as ground itch, a reddening and swelling of the affected parts accompanied by most intense itching.

That the skin is the most important portal of entry has been shown, for when the inhabitants of infected districts are compelled to wear shoes, the extent of the disease is greatly checked. The other phase of the hygienic control of the disease is the proper disposal of the excreta.

The diagnosis is easily made. A marked anemia due to the toxins formed by the worm is usually present; eosinophilia is the rule, if the anemia is not extreme. Large numbers of eggs are usually present in the feces; if they are few in number, the fecal material should be shaken up with a saturated solution of sodium chloride. The eggs float and with a pipette can be removed to the slide for microscopic determination.

Trichocephalus dispar (*Trichuris trichiura*).—The males and females are of nearly equal size, 4 to 5 cm. long. A little less than one-half of the body (the posterior portion) is about 1 mm. thick, and in the male is rolled into a flattened spiral, but in the female is but slightly bent. The anterior part of the body is very slender (Fig. 95) and is embedded in the mucous membrane of the host. The eggs are elongated, oval-shaped, about 0.05 mm. long and about one-half as wide, with a thick

brown capsule. The eggs of this parasite are frequently found; in France, in at least 70 per cent. of the stools examined; in London, in 7 per cent.; in parts of Germany, in 45 per cent.; in the United States, in 9 per cent.[1] The worm is commonly found in the cecum, usually in small, but sometimes in very large, numbers. It is generally of little pathological significance, commonly producing no symptoms, not even eosinophilia. The eggs require some months for development in water or moist earth. They are then transferred by uncooked food or soiled hands (as of miners, farmers, brickmakers) to the mouth; mature worms develop in about a month.

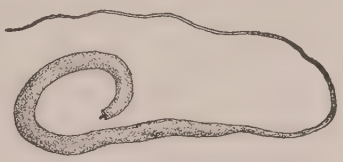


Fig. 95.—Trichocephalus Dispar.
From the skin of the mons veneris.

Trichinella spiralis (*Trichina spiralis*). —The female of this common[2] parasite is, in the mature condition, about 3 mm. long, the male from 1 to 1.5 mm. long; they are filiform in shape and white in color. The young are born in the form of tiny worms about 0.01 mm. in length and somewhat similar to the adult in shape. Infection occurs in man from the ingestion of insufficiently cooked pork. The muscle of the diseased pig contains the embryos of the parasite in an encysted condition. In the stomach the capsule of the worm is dissolved and the embryos are set free. They very rapidly mature, increasing in size, and the females give birth in the small intestine to very large numbers of young. It is estimated that a single female may give birth to from 1,300 to 1,500 young.

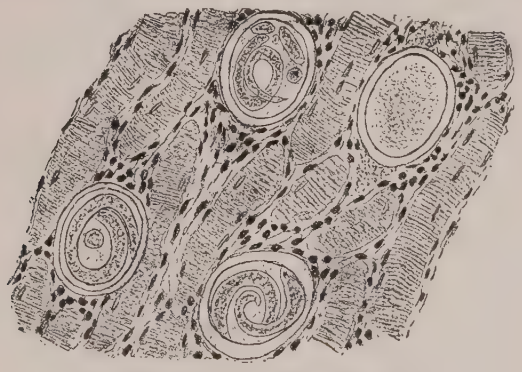


Fig. 96.—Trichinella Spiralis.
The parasites are encysted in muscle. In one capsule the parasite has died, and the granular material replacing it is calcified.

These find their way through the mucous membrane and wall of the gut, by way of the lymph-channels, into various parts of the body. In heavy infections the parasites can be demonstrated in the blood,[3] and occasionally in the spinal fluid,[4] in the latter case sometimes giving rise to clinical symptoms of meningitis.

[1] *French* and *Boycott*, Jour. Hyg., London, 1905, v, 274.
[2] *Williams*, Jour. Med. Research, 1901, N. S. i, 64.
[3] *Herrick, W. W.*, and *Janeway, T. C.*, Arch. Int. Med., 1909, iii, 263; *Stäubli*, Trichinosis, Wiesbaden, 1909.
[4] *Van Cott, J. M.*, and *Lintz, W.*, Jour. Am. Med. Assn., 1914, lxii, 680; *Meyer, J.*, ibid., 1918, **lxx**, 588 (bibl.).

After entering the circulation, they are carried to the voluntary striated muscle tissue, which they penetrate, and enter the muscle fibers. Here they cause a disintegration of the contractile substance, and coil themselves inside of the sarcolemma. In this situation they become encapsulated by material in part furnished by themselves, in part by means of the inflammatory reaction which their presence induces in the connective tissue of the muscle. The worms are surrounded inside the capsule by granular material (Fig. 96). The capsule after a time becomes partially calcified, and in this condition may be readily seen by the naked eye as a tiny white speck. In this encysted state they may remain inactive but living for an indefinite, often for a very long time. Most frequently the cysts contain but one embryo, but they may contain from two to four. The embryo may die and its remains become calcified.

The same course of events follows when the muscle trichinæ are eaten by the pig or a variety of other animals.

The embryos in the muscle are killed by a temperature of 55° C. and by some of the methods of curing pork.

The embryos may mature and a new generation be born within from five to eight days after the ingestion of the diseased meat.

As the result of the presence of these parasites in the body, if the invasion be severe, nutrition may be impaired and catarrhal enteritis, high fever, great pain in the muscles, bronchopneumonia, hyperplasia of the mesenteric lymph-nodes, and fatty degeneration of the liver may occur. Leucocytosis with a great increase in the number of eosinophile cells is common.[1] The bone-marrow is often hyperplastic and contains large numbers of cells with eosinophile granules. The encapsulated embryos may be found in enormous numbers almost exclusively in various voluntary muscles of the body, but they are most apt to be found, when not very abundant, in the muscles of the neck and larynx, in the intercostals and the diaphragm. They tend to collect toward the tendinous extremities of the muscles. Trichinæ also occur in the rat, cat, mouse, and other animals.

Dracunculus medinensis (*Filaria medinensis, Guinea worm*).—This is a thread-like worm, the female being sometimes as much as 80 cm. long and from 0.5 to 1.7 mm. thick. The male, which is rarely found, is much smaller, measuring only about 4 cm. in length. It is common in the East, and inhabits the subcutaneous connective tissue, in which it often gives rise to abscesses and ulcers. Eosinophilia is commonly present. The embryos live for a time free in fresh water, and are taken up by a species of fresh-water crustacean, in whose body they undergo further development, and by the ingestion of which the infection of the human subject occurs.

Filaria sanguinis hominis (*Filaria bancrofti*).—The larva of this parasite, which inhabits the blood and lymph of man, especially in Brazil, Egypt, and some parts of the Orient, and occasionally occurs in this country, is about 0.35 mm. long, rounded anteriorly, and pointed at the

[1] See *Brown, T. R.*, Jour. Exper. Med., 1898, iii, 315; and *Albert, H.*, Am. Jour. Med. Sc., 1910, cxl, 167.

tail (Fig. 97). It has about the diameter of a red blood-cell. It occurs, sometimes in great numbers, in the blood during the night time, being as a rule absent during the day. It may occur in the urine in connection with chyluria and hematuria. The mature female is from 8 to 10 cm. long, and has been found inhabiting the lymph-vessels of man, particularly in the scrotum and lower extremities. Owing to the obstructions which it causes in the lymph circulation, and to the local irritation which its presence induces, it sometimes gives rise to lymphangiectasis,[1] edema, abscesses, and elephantiasis. Such chronic lymph stasis induces chronic fibrosis of the subcutaneous tissues and thickening and ulceration of the skin (Fig. 97*a*). Eosinophilia is common. One of the embryonic stages of development is believed to take place in the body of a species of

Fig. 97.—Filiaria sanguinis hominis —Larval Form from the Blood.

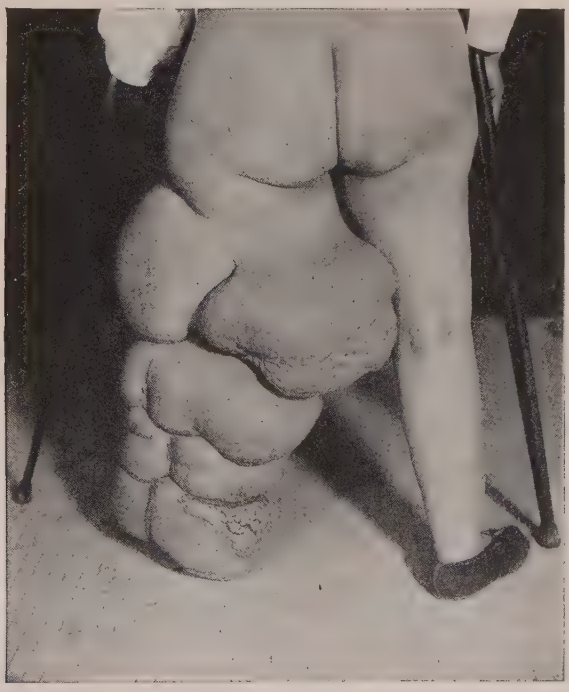


Fig. 97*a*.—Elephantiasis.
Patient of Dr. S. W. Lambert.

nocturnal mosquito. Through the bodies of the dead mosquitoes, which are liable to fall into the drinking-water, it is believed the spread of the parasite may occur.

[1] For a study of filarial lymphatic varix, see *Opie*, Tr. Assn. Am. Phys., 1901, xvi, 314.

There are several other species of filaria occasionally found in man which it is not necessary to enumerate here.[1]

Strongyloides stercoralis.—A small filiform worm, from 1 to 2 mm. in length, is found, often in enormous numbers, in the intestine and biliary and pancreatic ducts of man in Cochin China, Italy, and South and Central America, giving rise to endemic diarrhea. The adult worm lives in the mucous membrane of the small intestine; and the eggs hatch in the feces, so that only the rhabditiform larvæ are found. These pass out with the feces, penetrate the skin, like the uncinaria, and enter the intestinal wall, thus completing the cycle.[2]

Arthropoda.

The scope of this work does not permit us to enter in detail into the subject of external parasites, which will be found described in treatises on diseases of the skin or in the general works on parasites referred to below.[3] But, owing to their frequent occurrence and practical importance, we may briefly describe a few of the more common forms of arthropods.

The common "itch insect"—*Sarcoptes scabiei* (*Acarus scabiei*)—is shaped somewhat like a turtle, with a chitinous covering, and presents the general appearance seen in Fig. 98. The female is about 0.45 mm. long, the male a little smaller.

FIG. 98.—SARCOPTES SCABIEI—THE "ITCH INSECT." Female; back view. After Furstenberg.

FIG. 99.—PEDICULUS CAPITIS—THE "HEAD LOUSE." Male. After Braun.

The parasite bores little tunnels in the skin, in which the eggs are laid and the young hatched. After a few days these bore fresh channels in the skin. For their detection a bit of the superficial layer of the skin is snipped out with curved scissors, dehydrated and cleared up with oil

[1] See *Fülleborn*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, viii, 185.

[2] *Askanazy*, Centralbl. f. Bakteriol., Orig. I, 1900, xxvii, 569; *Price*, Jour. Am. Med. Assn., 1903, xli, 713.

[3] *Bibliography.*—Especially to be recommended for detailed description of human and animal parasites is the small work of *Brumpt*, Précis de Parasitologie, Paris, 2d ed., 1913.

Consult also, especially for the forms of eggs and other parts of animal parasites which may be found in the excreta, *von Jaksch*, *Wood*, or *Simon*, or other works on clinical microscopy.

The Reports of the Bureau of Animal Industry of the U. S. Department of Agriculture contain many valuable data relating to animal parasites and the diseases of animals in the United States.

See for a general study of the effects of parasites on their host, *Ward*, Science, 1907, xxv, 201.

of cloves, and examined under a low power, when the tunnels and the parasites, if present, will be readily visible.

The head louse, *Pediculus capitis*, is from 1 to 2 mm. long, the female being slightly the larger. The general appearance of the insect is seen in Fig. 99.

Pediculus pubis (*Phthirius inguinalis*) has recently become of hygienic interest as the possible carrier of the inciting agent of typhus fever.

Pediculus corporis or *vestimenti* has been considered as the carrier of relapsing and trench[1] fevers (pages 330 and 357).

The rat flea, *Xenopsylla cheopis*, a cosmopolitan parasite, is apparently the most important carrier of the plague.

Demodex folliculorum is an arachnoid parasite, frequently found living in the Meibomian and sebaceous glands, particularly of the face and of

Fig. 100.—Demodex Folliculorum.

portions of the eyelids. It has been stated that in the latter situation they incite an acute inflammatory lesion, but there seems to be no foundation for this assumption, and in all probability they are practically harmless. It has been suggested, however, on somewhat doubtful grounds, that there may be a connection between cancer and the occurrence of demodex in the skin.[2] The male parasite measures about 0.3 mm., the female about 0.4 mm. (Fig. 100).

[1] For experimental proof of the transmission by lice of the virus of trench fever, see Trench Fever, Report of Commission, Medical Research Committee, American Red Cross, Oxford, 1918.

[2] *Borrel, A.*, Ann. de l'Inst. Pasteur, 1909, xxiii, 97.

CHAPTER VII

PLANT PARASITES.

The plant parasites of man belong among the simplest of living organisms. Three distinct groups are of frequent occurrence in or upon the body. These are:

1. *Bacteria*, or fission fungi (Schizomycetes).
2. *Yeasts*, or yeast fungi, or sprouting fungi (Blastomycetes).
3. *Moulds*, or mould fungi (Hyphomycetes).

The first group, the bacteria, is of the greatest significance, because it contains organisms which are very frequently the excitants of serious disease.

The scope of this work does not permit more than a brief outline of the rapidly increasing knowledge of the forms, nature, and performances of the bacteria. For details we refer to special treatises on bacteriology.[1]

I. Bacteria.

MORPHOLOGY, PHYSIOLOGY, AND DISTRIBUTION.

Bacteria are minute unicellular plants devoid of chlorophyll, multiplying by transverse division and in some cases preserving the species by the formation of spores.

The colorless, sometimes granular protoplasm is inclosed by a membrane, and some forms are surrounded by a transparent capsule. Not

Fig. 101.—Bacteria with Flagella.

Fig. 102.—Typical Forms of Bacteria. Cocci, Bacilli, and Spirilla.

infrequently parts of the protoplasm appear less dense than the rest, as if from vacuolation, and a few observers have claimed to demonstrate in certain forms a nuclear substance.

Many of the bacteria, especially bacilli and spirilla, less frequently the cocci, have hair-like processes called *flagella* which are apparently organs of locomotion (Fig. 101). These may be single or in tufts; may be

[1] *Hiss* and *Zinsser*, Text-book of Bacteriology, 4th ed., New York, 1918; *Park* and *Williams*, Pathogenic Microörganisms, 8th ed., New York, 1924; *Kolle* and *Wassermann*, Handbuch d. path. Mikroorganismen, 2d ed., Jena, 1912–13; *Muir* and *Ritchie*, Manual of Bacteriology, 6th ed., London, 1913.

at one or both ends or over the general surface. Their number and distribution seem sometimes to be characteristic of special forms. (See *Motility* below.)

Forms of Bacteria.—Bacteria may be grouped in three classes (Fig. 102).

1. *Spheroidal bacteria.*—Cocci or micrococci (singular, coccus,[1] micrococcus).

2. *Rod-like bacteria.*—Bacilli (singular, bacillus).

3. *Spiral bacteria.*—Spirilla (singular, spirillum).

All straight bacteria which have one axis longer than the other are called bacilli, even though the form is oval rather than rod-like. The ends of bacilli may be square or rounded, and in stained preparations, in some cases, concave.

While the cocci elongate a little in preparation for fission and in this condition present a slight irregularity in the length of their axes, and thus resemble bacilli, the complete observation of their life cycle rarely permits error in the determination of the primary group to which a given microorganism belongs.

Variations in Form and Size.—Some bacteria present slight modifications of the fundamental form in certain phases of their growth and under various chemical and physical conditions. Thus some of the cocci after division are slightly flattened on their contiguous sides—biscuit-shaped; certain bacilli may bulge slightly in the middle—*clostridium* forms; others may be larger at one end than at the other—racket-shaped; bacilli from the same culture may present considerable irregularities in breadth and especially in length. The morphology may differ somewhat under different growth conditions. But these slight variations in form rarely give rise to serious difficulty in classification.

Fig. 103.—Bacteria with Capsules. (Pneumococcus.)

Finally, when bacteria are placed under conditions unfavorable for the maintenance of their life processes, and when they are dead, they are often irregularly swollen and contorted or may undergo partial disintegration, giving rise to what are known as "*involution forms.*"

While all bacteria are minute[2] there is among them considerable diversity in size, some being many times larger than others.[3]

Certain bacteria, those of the diphtheria group for example, contain deeply staining bodies called *metachromatic granules* the nature of which is as yet undetermined.

Reproduction of Bacteria.—When the bacteria are about to multiply by fission they elongate, a dividing septum forms, they become con-

[1] Pronounced *kok'-us*, plural *kok'-si*. The term *microorganism* includes all of these forms of minute and lowly plants. They are sometimes spoken of collectively as *germs* or *microbes*.

[2] Some forms, those for example inducing the pleuropneumonia of cattle, are beyond the present resolving power of the microscope—ultramicroscopic. For a review of ultramicroscopic bacteria or filterable viruses see *Wolbach*, Jour. Med. Research, 1912, N. S. xxii, 1.

[3] For convenience of expression microscopists have agreed to let the letter μ stand for the word micromillimeter, which is one-thousandth part of a millimeter. This unit of measure, equal to about one-twenty-five thousandth of an inch, is often called a *micron*.

stricted at a right angle to the axial elongation, and finally two independent organisms are produced. The multiplication of bacteria by fission may, when the conditions are favorable, occur so rapidly[1] as to give rise within a few hours to an enormous number of new individuals.

Aggregations of Bacteria.—In many cases, the new individuals thus developed fall apart in a form identical with that of the parent cell. In some species, on the other hand, the new-formed individuals are prone to cling together with greater or less tenacity, thus giving rise to growth aggregates which are more or less characteristic (Fig. 104). Thus among the cocci there are those in which a large part of the new individuals cling together in pairs. These forms are called *diplococci*. In others the pairs cling together in longer aggregates or chains. Such are called *streptococci*.

Fig. 104.—Growth Aggregates of Bacteria.

1, Diplococci; 2, streptococci; 3, merismopedia; 4, diplobacilli; 5, streptobacilli; 6, curved bacteria forming chains.

A similar occurrence in the bacilli gives rise to *diplobacilli* and *streptobacilli*. Some of the spiral forms are due to the close junction end to end of oppositely curved segments.

Certain cocci divide in two directions at right angles to each other, giving rise to four cocci clinging together and lying in the same plane. These are called tetrads or *merismopedia*.

Finally cocci may divide along three planes at right angles to each other, giving rise to cuboidal packets of eight germs or some multiple of this —such growth groups are called *sarcina*[2] (Fig. 105).

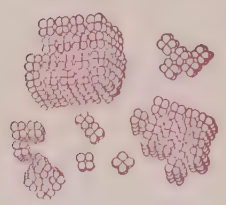


Fig. 105.—Sarcina.

Showing growth aggregates in cuboidal masses.

Higher Bacteria.—There is a family of filamentous or branching organisms which are often spoken of as *polymorphous* or *higher bacteria*, some of which may indeed be links between the bacteria and higher plant forms. Filamentous bacteria are more or less distinctly segmented, and the segments may be inclosed in a common sheath. The modes of reproduction and a certain specialization of function of different parts of the filaments which is frequently present indicate affiliations with higher forms. By this specialization of function is meant the attachment of the threads at one end to the substance on which they grow, and the formation at the free ends of structures which appear to be concerned in the reproduction. Several groups of these organisms have been named, but

[1] A. Fischer has estimated that the cholera spirillum may undergo complete fission at intervals of about twenty minutes so that a single organism might give rise under favorable conditions, could these be secured, to 1600 trillions in twenty-four hours.

[2] Bacteria in masses embedded in and held together by a more or less abundant homogeneous material which they elaborate are called *zoöglea*.

few of them have as yet been adequately studied. The groups *streptothrix, cladothrix, crenothrix, leptothrix* may be cited. Among these the *streptothrix* (*Nocardia*) is of the most significance here, since pathogenic forms are known.[1] The *Streptothrix actinomyces*, and closely related species, and the lesions which they induce, will be described later. There are many reasons for the belief that the forms called streptothrix and actinomyces are more closely related to the moulds than to the bacteria, but the scope of this work does not permit the discussion of the subject, particularly difficult as it is on account of the confusion of terms and the lack of sufficient knowledge of the life history of the organisms involved (see Actinomyces, page 268).

Variations in Forms.—Their apparently simple structure and the lowly position which bacteria occupy in the scale of living things have given rise to the conjecture that marked changes in form within the limits of the primary groups, or even changes from one primary group to another, may be brought about by alterations in environment, food, etc. In the early days of the exact study of bacteria this belief in *pleomorphism* in bacteria found ready currency. But the more exact study of separate forms, which the new technique has made possible, has led to the general acceptance of the view that variations do not occur except within comparatively narrow limits, and that what we are accustomed to call species of bacteria maintain their morphological characteristics with tenacity under the most varied changes in environment, even though these persist through the countless generations which may pass within the limits of a single experiment. The physiological characters of bacteria are, as we shall presently see, subject to wide and significant variation, but, so far as we can now see *monomorphism* widely, if not exclusively, prevails.

Spores.—Under a variety of conditions, the limitations of which are not very well understood, the species is perpetuated, not by simple division, but by the development of *spores*. The most common mode of spore formation is called *endogenous*. A small, shining mass makes its appearance within the protoplasm from which it is formed, grows more and more distinct, and finally appears as a sharply defined spheroidal or oval, strongly refractile colorless body surrounded by a limiting membrane (Fig. 106), which can be separately stained and may remain within a cell membrane or may free itself by degeneration of the latter. Endogenous spore formation is common in bacilli, rare in spirilla and in cocci. The spores appear to be surrounded by a dense envelope, and are, as a rule, much more resistant to deleterious agencies, such as heat, drying, chemicals, etc., than are the vegetative forms of the bacteria themselves.

FIG. 106.—BACILLI SHOWING SPORES.

The bodies of the bacilli are stained with methylene blue, the spores with fuchsin.

Spores, when placed under favorable conditions in the presence of moisture and nutriment, swell, become less refractile, and develop into

[1] Some organisms commonly called bacilli—tubercle bacillus for example—may belong in this group.

the usual vegetative form. The actual observation of this transformation is, in doubtful cases, the only absolute guarantee of the spore nature of these bodies, though staining methods are useful. Another method of sporulation—*arthrogenous*—has been described, but its nature is not well understood.

Motility.—Some bacteria are capable of performing rapid movements, others are not; and the same form may be at one time motile and at another immotile, depending upon external conditions. Movement is largely confined to the rod-like and spiral forms, but has been observed in the spheroidal.

It has been shown that certain of the motile bacteria, when suspended in fluids, are attracted toward, or repelled from, dissolved chemical substances. This is called chemotaxis (see page 105), and it is termed positive or negative according as the organisms are attracted or repelled.

Conditions of Life, Growth, and Multiplication.—The bacteria require for their nutrition carbon, hydrogen, oxygen, and nitrogen, and certain mineral salts. These they can obtain from proteins and carbohydrates. Free oxygen is necessary for the growth and activities of some forms of bacteria and not for others.

Nitrogen may be obtained by some bacteria from inorganic salts of ammonia, from nitrites and nitrates. Bacteria grow best as a rule in an organic food medium, especially soluble albuminous material which is neutral or slightly alkaline. Most of these materials are rendered available as food by the action of enzymes—inverting, sugar-splitting, proteolytic, etc., often given off by the organisms and acting upon the albuminous materials.

Those bacteria which require free oxygen are called *aerobic*. Those which do not grow in its presence are called *anaerobic*. But between these extremes there are forms which make shift to grow without oxygen under favorable conditions, though they make use of it when present; others grow in its presence, though flourishing best in its absence: these are called *facultative* aerobes or *facultative* anaerobes, in distinction from those first mentioned, which we call *obligate* aerobes or anaerobes.

Bacteria are active only in the presence of moisture. When this and other conditions favoring their activity fail they do not necessarily die; some forms may remain, either as spores or as fully developed organisms, for long periods dry and inert, but capable of resuming their activity whenever they are again restored to favorable conditions.

Effects of Temperature, Light, etc.—Some bacteria are and some are not very sensitive to changes of temperature. At a temperature below +5° C. they are incapable of marked activity or proliferation. At +7° C. a slow growth has been observed in various species. Many forms may remain alive for long periods frozen in ice, while some are not killed by a temperature of −250° C. As the temperature is raised their activities increase up to a certain point. It may be said in general that they are most active at about the temperature of the body, although species differ considerably in this respect. In fluids many bacteria are killed by a prolonged exposure to a temperature of from 50° to 70° C. or even less.

On the other hand, certain species grow at a temperature of from 60° to 75° C. Such are called *thermophilic* bacteria. When dry they resist much higher temperatures than when moist. All known bacteria, save a few very invulnerable spore-forming species, are killed by a short exposure in the presence of moisture to a temperature of 100° C. The spores are, as a rule, more resistant to high temperatures than the bacteria themselves, some having been exposed, dry, to a temperature of 140° C. without destruction of life. Fluids containing the spores of bacteria which resist very high temperatures may be sterilized by boiling for a short time, then being allowed to stand at ordinary temperatures for several hours, and then again boiling; this process being repeated several times. In this way, although the spores themselves are not killed by the heat, the bacteria into which, if the conditions be favorable, they develop during the intervals are killed, so that finally the medium is entirely freed from both living spores and adult bacteria. Strong light is in general inimical to the life and growth of bacteria, and by direct sunlight many forms are readily killed. Ultraviolet rays in sufficient intensity and of wave lengths such as are given off by a quartz mercury arc, kill bacteria almost instantly. Various physical agents, such as ionic discharges from high voltage terminals, radium, and Roentgen rays, have some destructive action. Rapid and continuous shaking of fluids containing bacteria may kill the organisms.

Germicides.—Certain chemical agents, when brought into contact with bacteria, greatly reduce their activities or destroy their life altogether; but different species differ greatly in their capacity of resistance to these agents. The spores of certain bacteria are exceedingly resistant, much more so than the bacteria themselves, to the action of disinfecting agents. Among the chemical substances commonly used as disinfectants may be mentioned formaldehyde, carbolic acid, mercuric chloride and especially solutions of free chlorine, which are very inimical to the life of most bacteria and their spores, even in extremely dilute form.

Metabolism of Bacteria.—The metabolism of bacteria may be destructive or constructive. Their destructive or catabolic activities find expression in the fermentation of carbohydrates and in the cleavage of proteins and fats. Their constructive or anabolic activities are exemplified by their building up of nitrogenous compounds in the soil. We cannot here enter into the details of these processes, which must be sought in special treatises.

But it may be said in brief that a large number of complex chemical substances are elaborated during the growth of bacteria, their nature varying with the species of bacteria and the composition of their nutrient material. Some of the chemical compounds set free by the growing bacteria are bad-smelling or aromatic; some are inert and harmless substances; some are powerful poisons, and may, when they have accumulated in the fluids where they grow, inhibit activity and growth or even destroy the bacteria which have produced them.

Fermentations and putrefactions are due to the activities of micro-

organisms, some to bacteria, some to yeasts, some to moulds. Putrefaction is a form of fermentation in which nitrogenous compounds are decomposed by microorganisms setting free, especially in the absence of oxygen, bad-smelling substances.

Bacteria which induce fermentation are called *zymogenic*—and each species induces fermentation of a particular character in the presence of a special substance, as glucose, or members of a certain class of substances such as carbohydrates. Some of these fermentations are important in the arts; some are concerned in the changes which food products undergo under natural or artificial conditions, such as the development of koumyss from milk and the common butyric, lactic, alcoholic, and other fermentations.

The chemical changes which are induced by microorganisms in the process of fermentation are extremely complex and little understood.

Bacteria may develop, in their metabolic activities, soluble ferments[1] or *enzymes* of various kinds resembling diastase, pepsin, trypsin, rennet, etc. These may remain in the bacterial cell or may be diffused into the surrounding media. It is through these enzymes that the fermentations and protein, or rather amino-acid, cleavages so characteristic of many phases of bacterial metabolism are carried on.

Many bacteria form pigments as they grow (*chromogenic* bacteria). This pigment may be developed in or upon the germs themselves or may be diffused through the surrounding media and may be developed only in the presence of light, oxygen, etc. Gas-producing bacteria are called *aerogenic*. Certain species when growing in masses emit a phosphorescent light—*photogenic* bacteria.

Bacterial Poisons.

Ptomaines.—Certain basic chemical compounds which are formed by the action of bacteria upon various kinds of organic matter are called *ptomaines*.[2] Some of the ptomaines resulting from the breaking up of the protein molecule by bacteria in decomposing meat, fish, etc., are poisonous, though not apparently of as much importance as was once believed. But ptomaines should be distinguished from the true toxins now to be considered.

Toxins.—True bacterial *toxins* are poisonous substances produced by bacteria. They are probably highly toxic proteins with some analogy to the enzymes, and, like the secretory and excretory products of the body-cells, may be given off during the metabolic activities of the bacteria, in artificial cultures as well as in infective processes. The poisonous substances elaborated in the growth of the diphtheria and the tetanus bacilli are typical toxins. These toxins are especially characterized by their capacity to stimulate the body-cells, when the latter are called upon

[1] See *Bayliss*, Nature of Enzyme Action, 3d ed., New York, 1914. Also, for technique, *Wohlgemuth*, Grundriss der Fermentmethoden, Berlin, 1913. See, for studies showing inability of many bacteria to cleave native proteins, *Rettger*, *Berman*, and *Sturges*, Jour. Bacteriol., 1916, i, 15.

[2] The terms ptomaine and leucomaine are falling into disuse as the chemical structure of many of the toxic bases is being elucidated. See *Barger*, The Simpler Natural Bases, New York, 1914.

to adapt themselves to their presence, to the formation of antibodies (see page 207).

Endotoxins.—On the other hand certain bacteria which develop toxic qualities do not set these free as they are formed but store them in or build them into the structure of their bodies whence they are freed only after the death or disintegration of the bacterial cell through autolysis or some external agency. Such toxic substances stored in the texture of the bacteria are called *endotoxins* and they do not appear directly to stimulate the organism to the formation of antibodies, although the bodies of the bacteria have specific antigenic powers due to their characteristic proteins.

It is not certain, however, from present knowledge, whether these so-called endotoxins are strictly comparable with the toxins given off by bacteria of the type of the Bacillus diphtheriæ or Bacillus tetani. They are, if of truly toxic nature, much more firmly bound to the protein molecule of the organism, and are not separable by mechanical or chemical means. The toxic action seems to be released only when the bodies of the bacteria of this group are dissolved by the ferments of the blood and tissues, and the proteins thus set free from combinations with the cells of the host. When this has been accomplished, they give rise to the usual types of antibodies, agglutinins and bacteriolysins, and may also induce anaphylaxis.

When the bacterial proteins are split, it is possible that, in addition, certain non-specific general protein derivatives are produced, wholly independent of the type of organism giving rise to the infection, and that general protective substances may be formed in response. This is illustrated, for example, by the beneficial therapeutic results often seen following injections of killed typhoid bacilli in chronic streptococcus infections in man.

The important thing to remember in this connection is that it is through the action of these substances, whether soluble and eliminated during the life and functional activities of the bacteria or stored up in their bodies to be set free only upon their disruption, that the most striking damage is wrought in the organisms when body-cell and bacterial cell strive to adapt themselves to one another in the processes of infection which we are presently to study.

It is probable that there is still another group of non-specific toxic substances derived not directly from the bacteria but from the action of certain products of bacterial metabolism upon amino-acids of the blood and tissues, so that it may be through these secondary toxic products that some of the serious manifestations of infection and intoxication are induced.

The Rôle of Bacteria in Nature.—The bacteria play a very important rôle in nature in virtue of their power of feeding upon and decomposing dead organic material. A part of the new chemical compounds which are thus formed may be used by the bacteria for the purposes of their own nutrition and growth, while the rest are set free to serve, sooner or later, as food for other forms of plants or animals. In the decompositions

which are brought about in nature by the bacteria those compounds of nitrogen and carbon dioxide are set free which are essential for the nutrition of the higher plants.

Without the activities of bacteria, life could not be long maintained upon the earth, since the necessary carbon, hydrogen, oxygen, and nitrogen would soon be permanently locked up in unavailable form in organized material. Through the action of the various nitrifying bacteria in the soil, ammonia is decomposed with the formation of water and nitrous acid; nitrous is converted into nitric acid. The so-called denitrifying bacteria reduce nitrates to ammonia and to nitrites. In these ways, among others, water percolating through the soil may be freed from objectionable organic compounds. There are certain soil bacteria which aid special groups of plants to fix nitrogen from the surrounding media and make it available for the uses of the plant.

Distribution of Bacteria.—Bacteria are widely distributed in the air, in water, and in the superficial layers of the soil, where they may be present in enormous numbers. They are especially abundant among the habitations of man, or wherever under favorable conditions of moisture and temperature animal or vegetable substances are undergoing decay. They cling tenaciously to moist surfaces, but when dried, and especially when dried upon comminuted material, they may float in the air as dust. In quiet air they gradually settle with other forms of dust on to horizontal surfaces, and thus in closed, still rooms the bacteria-laden air may in a few hours almost wholly free itself of its living contaminations by a process analogous to sedimentation in water.

This wide-spread transportation of bacteria as dust by moving air, and the spontaneous cleansing of the latter by the settlement of the germs, are important factors in the sanitary problems which the complex conditions of modern life present.

While bacteria may live for long periods in the dried state in dust they do not in this condition multiply. But the upper three or four feet of the soil forms the great abiding, and when moist, the breeding place of the myriads of germs which are concerned in the salutary work of food preparation for higher plants. Large numbers of mould spores are frequently mingled with the bacteria in dust and soil.

Surface waters almost always contain bacteria, which may have entered by aerial dust or from the wash of adjacent soil or from direct human or animal contamination. Many bacteria find in water favorable conditions of life and flourish on what to other forms would be but scanty nutriment. Many pathogenic bacteria may remain alive for considerable periods in water, but they do not usually thrive there.

The water which in many places lies in hollows of the rocks, bathing the deeper layers of the soil or gathered in caverns and recesses beneath, is called *ground water*. This under favorable conditions is almost wholly free from microorganisms; these, through the complex processes of filtration, germ metabolism, etc., which go on in the upper soil layers, having, together with inorganic contaminations, been largely retained or transformed as the surface water has slowly sought the lower levels.

The Relationship of Bacteria to Other Living Beings.—So far as we know, with few exceptions, the bacteria whose natural habitat is the soil or air or water are not, under usual conditions, harmful to man. On the other hand, it is germs from the bodies of men or animals who are the victims of infectious disease, gaining access in one way or another to these great reservoirs and sources of distribution, which occasionally render the bacterial flora of soil and air and water of direct personal significance.

It will be seen from what has been said about bacteria and their various modes of life that some live in or upon and at the expense of other living beings—the hosts; these are *parasites*. Others which live and grow apart from a living host are called *saprophytes*. In either class there are forms which, through the capacity of adapting themselves to their environment, can maintain at one time a parasitic, at another a saprophytic life. Such germs are called, respectively, *facultative* parasites or *facultative* saprophytes. Those, on the other hand, whose life is strictly limited to the parasitic or saprophytic condition are called *obligatory* parasites or saprophytes.

Not all the bacteria which live in or upon the bodies of men and animals are in the stricter sense parasites. The terms *messmates* and *commensals* have been applied to such organisms as simply live with, but do not necessarily derive nutriment from, the host.

In some cases parasitic life on the part of the microorganism may contribute to the welfare of the host. This is the case in some bacteria which live upon the roots of certain leguminous plants, to whose nutrition they contribute by rendering atmospheric nitrogen directly available for the host. This condition of life is called *symbiosis*.

Species and Varieties.—As has already been indicated, the morphological characters of bacteria are so little subject to permanent variation under the widest diversity in the conditions to which they are subject that we are justified in the belief in fixed species. But so susceptible to external conditions are the functional activities of many species that not only is the occurrence of what may be called varieties within specific limits frequent under natural conditions, but more or less permanent variations may be experimentally produced.

Modifications of Functional Characters.—Almost all of the functional activities of bacteria upon which we rely as descriptive characters may be experimentally altered; thus the color-producing capacity may be diminished, the peptonizing and fermentative activities lowered, the pathogenic powers reduced or exalted, and even the capacity for spore formation abolished.

These more or less permanent modifications of function in bacteria may be induced by artificial cultivation under adverse conditions of temperature and nutrition, by the presence of deleterious chemical agents, antiseptics, etc., or by association with the body-cells and juices in susceptible or insusceptible animals.

Recent investigations have shown not only that many of the strict classifications of bacterial species must be abandoned, as suggested above, but also that within a pure line of organisms of very definite characters extraordinary variations in type of growth, virulence toward animals and capacity to act as antigens may occur. For example, when pure strains of the colon-dysentery group are cultivated under various conditions, two types of colonies may often be separated, one rough, the other smooth, with corresponding difference in their cultural and other biological features and their serological interreactions. These phenomena of "dissociation," as they have been termed, involve then the partial or total transformation of a pure line culture of standard type into one or more sub-types often differing in cultural, morphological, serological and biochemical characters from the original. The phenomenon may result in the disappearance of the mother culture, lysis of the old culture mass taking place over considerable areas of the growth. Such dissociation may occur spontaneously or may be induced by appropriate measures. Dissociation reveals itself on solid culture medium in a variety of ways. There may be a secondary colony formation with or without erosive action. There may be lysis or transformation over large or small areas with erosive features. One set of colonies may be much more translucent than others. The consistency of the colonies may vary and the morphology of the organisms in them be greatly different from that of the primary culture.

A curious phenomenon occasionally observed has received the designation of "suicide culture." A luxuriant growth may take place in the first twenty-four hours which then melts away until nothing is left but a thin transparent film covering the former site of the originally abundant growth.[1] These suicide cultures suggest the phenomenon first observed by Twort in 1915.[2] In studying cultures from calf vaccine virus the tubes often show "watery-looking areas, and in cultures that grew micrococci it was found that some of these colonies could not be subcultured, but if kept they became glassy and transparent. On examination of these glassy areas nothing but minute granules, staining reddish with Giemsa, could be seen." If plate cultures were made from the condensation water the colonies soon started to turn transparent and the micrococci were replaced by fine granules. "This action, unlike an ordinary degenerative process, started from the edge of the colonies, and further experiments showed that when a pure culture of the white or the yellow micrococcus isolated from vaccinia is touched with a small portion of one of the glassy colonies, the growth at the point touched soon starts to become transparent or glassy, and this gradually spreads over the whole growth, sometimes killing out all the micrococci and replacing these by fine granules." "The transparent material when diluted with saline passes the finest porcelain filters and in minute quantities prevents the continuous growth of the micrococci. This condition or disease of the

[1] For an elaborate study with a very complete bibliography of the phenomenon of bacterial dissociation, see *Hadley, P.*, Jour. Infec. Dis., 1927, xl, 1.

[2] "An investigation on the nature of ultramicroscopic viruses," *Twort, F. W.*, Lancet, 1915, pt. 2, 1241.

micrococcus when transmitted to pure cultures of the micrococcus can be conveyed to fresh cultures for an indefinite number of generations; but the transparent material will not grow by itself on any medium."

"On the whole, it seems probable, though by no means certain, that the active transparent material is produced by the micrococcus, and since it leads to its own destruction and can be transmitted to fresh healthy cultures, it might almost be considered as an acute infectious disease of micrococci." Similar results were obtained by Twort in the typhoid-colon group of organisms.

Without knowledge of this work d'Herelle, studying a case of convalescent Shiga dysentery, filtered a broth culture of the stools through a Chamberland candle and added this filtrate to a cloudy suspension of the Shiga bacillus. The culture was placed in the incubator and after a few hours became transparent. The study of the phenomenon of bacterial lysis thus led to the discovery of what is known as the bacteriophage by d'Herelle.[1] He believes that the phenomenon is due to an ultramicroscopic organism preying upon the bacteria. Bordet and others[2] see in the phenomenon only an inheritable spontaneous autolytic process. However, the extraordinary scientific and therapeutic possibilities dormant in this discovery may make it one of the most important since the study of bacteria was begun by Pasteur.

Twort draws a sharp distinction between ultra-microscopic organisms and what he calls ultra-scopic viruses. He believes that there must be in nature an enormous number of wild or non-pathogenic filterable viruses and in his opinion these are transitional, evolutionary filter-passing phases between the unorganized ferment and the bacteria. In other words, they represent a lower pre-cellular form of protoplasm which still has a certain existence and preys upon the higher forms. These hypothetical substances constitute the long series of pre-cellular ancestors back of the simplest unicellular organism. Twort virtually assumes a phase of pre-cellular or pre-bacterial existence in which the molecule of some complex organic substance becomes a true biological molecule, combining with other particles to form a relatively large mass of plasm.[3] It has been suggested that the hypothetical virus of cancer recently announced by Gye and Barnard[4] belongs in this group. According to Barnard, the material particles which he is able to photograph in the cultures of the virus by the use of ultra-violet light are only some three times the size of a molecule of hemoglobin, but the fact that there is some formed organic material in such cultures is, as has been pointed out by Barnard, no proof that these bodies are true organisms. They may be mere agglomerations of protein substances and have no function as the etiologic agent of cancer.[5]

[1] For the latest summary of this interesting phenomenon see *d'Herelle*, Le bactériophage et son comportement, 2d ed., Paris, 1926. *Bull*, Physiol. Reviews, 1925, x, 95.

[2] *Bordet, J.* and *Ciuca, M.*, La bactériophage de d'Herelle, sa production et son interpretation, Compt. rend. Soc. de biol., 1920, lxxxiii, 1296. *Bordet*, Ann. Inst. Pasteur., 1925, xxix, 717.

[3] *Twort*, Jour. of State Med., London, 1923, xxxi, 351.

[4] *Gye* and *Barnard*, Lancet, 1925, ccix, 109.

[5] For further details of the methods used in ultra-violet photomicrography, see paper by Barnard in Dict. of Applied Physics, vol. iv, p. 237–245 (bibl.).

CLASSIFICATION OF BACTERIA.

The beginning of the systematic study of bacteria by exact and reliable methods is of such recent date, they are so minute, and our present optical apparatus reveals so few differential morphological characters, and so few, withal, of the many existing forms have as yet been studied, that a satisfactory classification or nomenclature of the bacteria is not yet possible.

Outside of the limit of the primary classes above described and based upon the form, position of flagella, and motility, we are obliged to use for the purposes of identification and description the results of physiological activities which the special forms of bacteria display when placed under diverse and usually entirely artificial conditions of food, temperature, and general environment. It is evident from this condition of affairs that what in our attempts at classifications we are wont to call genera and species, are not such in the strict sense in which these terms are used in other domains of biology. That which corresponds to the generic name in the more exact vocabularies is in ours usually the growth form which indicates the primary class to which the germ belongs, as coccus, bacillus, or spirillum, or some growth modification of this, as diplococcus, streptococcus, streptobacillus, and the like. To this is usually appended a more or less distinctive specific name, which ordinarily indicates some noteworthy physiological capacity of the germ, such as its peptonizing power, the pigment which it elaborates, some prominent chemical reaction which it initiates, some marked effect upon an artificial culture medium, its disease-producing power in men or animals, or some fact about its habitat, or the situation in which it was found. All of these and other heterogeneous characteristics, largely functional, which may be developed under natural or artificial conditions, constitute data in the life history of germs upon which the classification and nomenclature of bacteria are at present based.

Notwithstanding the value of this principle of grouping and nomenclature, its inadequacy even for temporary use is becoming painfully evident as research proceeds, partly because of the large variations to which physiological activities are liable, and partly because we cannot always sharply distinguish between races, varieties, and species.

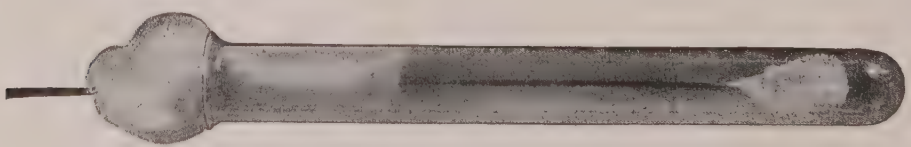


FIG. 107.—STERILIZED COTTON SWAB IN A STERILIZED TUBE, FOR COLLECTING FLUIDS CONTAINING BACTERIA.

Collection of Material for Bacterial Cultures.

Material obtained from the human body which is to be subjected to bacterial examination should be collected with every precaution against accidental contamination.

A convenient mode of collection and transportation of small quantities of fluid or semi-fluid material, such as exudates, discharges, etc., for purposes of bacterial examination is to twist a small wad of absorbent cotton on to the end of an iron or steel wire

about five inches long, put this, swab end foremost, into the tube (Fig. 107), plug the mouth with cotton, and sterilize the whole in a dry oven for an hour at 160° C.

Several of these cotton swabs may be prepared at once and kept on hand. The swab, carefully removed and saturated with the material to be examined, is at once returned to the tube; this is plugged, and may be thus safely transported.[1]

II. Yeasts.

These microorganisms—larger than bacteria and mostly saprophytes—consist of oval or spheroidal cells with granular protoplasm and a thin membrane. They multiply by sprouts or buds from the parent cell (Fig. 108). The new individuals may separate from the old, or may cling to them so that chain-like combinations may occur. They sometimes form endogenous spores, known as ascospores. Some species develop bright colors in their growth.

Fig. 108.—Yeast Saccharomyces.

There are many forms of yeasts which are concerned in various phases of fermentation. Some of these, alcoholic fermentation for example, are of great economic importance.[2] Certain forms of yeasts flourish in the stomach during digestive disorders and in the bladder in diabetes without inciting lesions. Various yeasts have been proved to be pathogenic in lower animals and in man.[3]

Coccidioidal Granuloma.[4]—Infection with the *Coccidioides immitis* is rare, only twenty-four cases having been published up to 1914. It occurs almost exclusively in adult males, most of the patients having been day-laborers, and the majority of cases have been reported in the San Joaquin Valley, California. It is probably not spread from person to person as in ordinary contagious disease, but rather seems to be acquired from some external source, possibly from domestic animals or through the bite of some insect. Judging from the clinical and pathological evidence the portal of entry of the parasite into the body is through the skin in many cases, by inhalation or by ingestion in others; but there is still much obscurity in regard to the definite mode of infection. The prognosis is very grave; in only two of the twenty-four cases recorded is recovery known to have occurred. The clinical course of the disease has shown little constancy; but there is usually a more or less irregular fever. Some of the skin lesions resemble mycosis fungoides. Slow, painless, subcutaneous abscesses have occurred in several cases; in others, glandular lesions imitating tuberculosis have been noticed. Invasion of the bone in various portions of the body, acute pulmonary symptoms, and meningitis

[1] For further suggestions for the collection and examination of specimens for microorganisms, and for references to studies on the bacteria of the human body, see pp. 175 and 176. For methods of morphological study of bacteria, see *Hiss* and *Zinsser*, Text-Book of Bacteriology, 4th ed., New York, 1918; *Park* and *Williams*, Pathogenic Microorganisms, 8th ed., New York, 1924; and *Kolle* and *Wassermann*, Handbuch d. path. Mikroorganismen, 2d ed., 1912–13.

[2] For a consideration of the relationship of microorganisms to various forms of fermentation, with bibl., consult *Jörgenson*, Microorganisms and Fermentation, Eng. Transl., 1900.

[3] *Stoddard, J. L.*, and *Cutler, E. C.*, Torula infection in man, Monograph No. 6, Rockefeller Inst., New York, 1916; *Pierson, P. H.*, Jour. Am. Med. Assn., 1917, lxix, 2179.

[4] *MacNeal, W. J.* and *Taylor, R. M.*, Jour. Med. Research, 1914, N. S. xxv, 261 (bibl.); also *Brown, P. K.*, and *Cummins, W. T.*, Arch. Int. Med., 1915, xv, 608; and *Cummins, W. T.*, and *Sanders, J.*, Jour. Med. Research, 1916, N. S. xxx, 243.

have been described. Several instances of acute generalized infection without localization and in a general way resembling typhoid fever have been seen. Microscopically the lesions resemble those of tuberculosis, and can be distinguished only by noting the presence of the spherical parasite with double contoured wall and filled with a granular protoplasm, sometimes vacuolated, sometimes segmented. The segmentation or endogenous spore formation and absence of budding permits its distinction from the *Cryptococcus dermatidis* described by Gilchrist[1] and more usually known as Blastomycetes or Oidiomycetes. While the exact classification of the parasite is still under discussion, it is unquestionably a fungus. The organism as it occurs in the body is a doubly contoured sphere varying from 5 to 50 micra or more in diameter. The capsule is hyaline, and varies from 1 to 5 micra in thickness. Within the cell is a

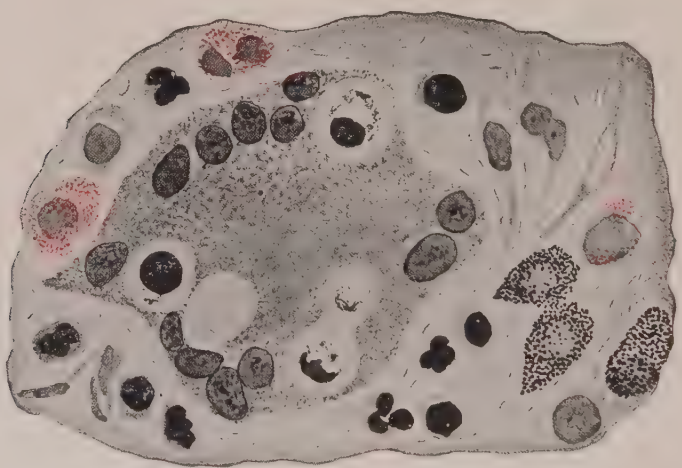


FIG. 109.—OIDIOMYCOSIS CUTIS—*Blastomycotic dermatitis.*
From skin lesion, showing giant cells containing the oidium with mast cells and eosinophile cells in the adjacent tissue just beneath the epithelium.

granular protoplasm, vacuolated, or segmented into numerous irregular daughter cells. In some cases a large sphere may be found, filled with numerous smaller spheres each surrounded by its individual capsule. Ruptured capsules are commonly found in the lesions; but the small parasites, either naked or encapsulated, which have escaped from these larger capsules, are not ordinarily recognizable until they have enlarged somewhat and the distinguishing capsule has developed. The parasite grows either aerobically or anaerobically. In the aerobic cultures made upon suitable media, mycelium develops.

The extrahuman habitat of Coccidioides immitis is not known. Many animals are susceptible to inoculation, guinea-pigs, rabbits, and monkeys being most conveniently employed for experimental work.

[1] *Gilchrist* and *Stokes*, Jour. Exper. Med., 1898, iii, 53.

Blastomycotic dermatitis[1] (Oidiomycosis) is a localized inflammation, papular and pustular in character, leading to warty outgrowths, to the formation of abscesses beneath the skin, and to ulcers. Deeper parts, such as bone, may be involved. Hyperplasia of epithelium and development of granulation tissue beneath with the formation of giant cells (Fig. 109), mast cells, and eosinophilic cells may be associated with the local growth of the blastomycetes and the formation of abscesses, the latter often intraepithelial. The local lesion may extend to the involvement of large areas of skin and subcutaneous tissue.

The organism—Oidium—is present in the involved tissues as a rounded double contoured body (Fig. 110), varying in diameter from 10 to 20 micra. It sometimes buds and contains various rounded refractile or granular structures. These organisms may be inclosed in a homogeneous jelly-like mass. They are readily cultivated in artificial media and can be successfully inoculated into animals, such as the guinea-pig.

FIG. 110.—OIDIUM FROM A CASE OF OIDIOMYCOSIS CUTIS (Blastomycotic dermatitis).

Generalization of the blastomycotic infection may take place and be fatal. In the systemic disease the lungs, spleen, and kidneys are especially involved in the formation of abscesses and local tissue hyperplasia containing the organism.[2]

Thrush.—A microorganism, related to both the fungi and the yeasts, and frequently found in the mouth, fauces, and esophagus of children, in the form of a whitish pellicle, is the so-called *Oidium albicans*, which consists of branching, jointed threads and spores which penetrate between the epithelial cells. This fungus may assume considerable importance, when in very feeble children it blocks the esophagus, or when, as is rarely the case, from the surface of ulcers it penetrates the blood-vessels and gives rise to visceral metastasis.

A tropical disease called *sprue* is thought to be due[3] to a distinct species, *Monilia albicans*.

III. Moulds.

The moulds are considerably more complex in structure than either the bacteria or the yeasts. Some of the forms are very common and universally known. In general, it may be said that the moulds consist of a series of delicate, translucent, branching jointed threads—*mycelium*—usually giving rise to *hyphæ*, from which, either directly or in more

[1] *Gilchrist*, Johns Hopkins Hosp. Rep., 1896, i, 269. For a résumé of pathogenic blastomycetes with experiments and bibl., see *Fullerton*, Jour. Path. and Bacteriol., 1900, vi, 37; *Sternberg, C.*, Zieglers Beitr., 1902, xxxii, 1; *Ricketts, H. T.*, Jour. Med. Research, 1901, N. S. i, 377; *Otis* and *Evans*, Jour. Am. Med. Assn., 1903, xli, 1075; *Bassoe*, Jour. Infect. Dis., 1906, iii, 91; *Irons* and *Graham*, ibid., p. 666; and *Stober, A. M.*, Arch. Int. Med., 1914, xiii, 509.

[2] *Fontaine, Hasse*, and *Mitchell*, Arch. Int. Med., 1909, iv, 101.

[3] *Ashford, B. K.*, Am. Jour. Med. Sc., 1915, cl, 680; *Wood, E. J.*, ibid., p. 692; and *Nicholls, L.*, Jour. Trop. Med., 1919, xxii, 21.

complex forms through the intervention of a special structure, the *sporangium*, the spores are developed (Fig. 111). The moulds which are apt to occur in the human body may be of the former, more simple, or of the latter, more complex, type.[1] Among the simpler forms of moulds which occur in the body may be mentioned the Achorion Schönleinii, Microsporon furfur, Trichophyton tonsurans. There is a close morphological resemblance between these forms.

Fig. 111.—Aspergillus Glaucus.
Showing mycelium, from which arise the spore-bearing structures, the sporangia, borne upon the hyphæ.

The Favus Fungus (*Achorion Schönleinii*), is formed of a much-branching mycelium from which the spores are directly developed (Fig. 112). It grows readily on artificial culture media, such as nutrient agar and gelatin, at the temperature of the body. This fungus is most apt to grow upon the hairy part of the head, where it forms small surface crusts and grows into the shafts and root sheaths of the hair, exciting inflammation in the adjacent tissue.

Ringworm (*Tinea circinata; Herpes tonsurans*).—The inciting agents of this readily communicable disease are several species of *Trichophyton tonsurans*, which develops in the form of a moderately branching mycelium, forming comparatively few spores. It grows in the skin, either about or apart from the hairs, or in the nails, inducing the lesions of various phases of ringworm which differ considerably, depending upon the particular structures involved. At body temperature it grows readily on artificial culture media, differing markedly in appearance from Achorion.

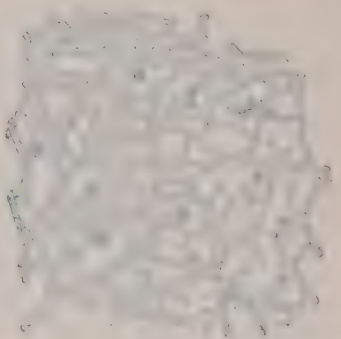


Fig. 112.—Achorion Schonleinii—Favus.
From a culture.

Pityriasis versicolor.—*Microsporon furfur*, the mould fungus causing pityriasis versicolor, is more prone than the Achorion to the development of many spores, but otherwise considerably resembles it morphologically. It grows with some difficulty on artificial media. By its infiltration of the epidermis, especially of the body and upper extremities, it causes larger and smaller yellowish or brownish patches.

The Higher Moulds.—The more complex types of moulds are only

[1] See *Renon*, Etude sur l'aspergillose chez les animaux et chez l'homme, Paris, 1897; *Leopold* and *Levi*, Gaz. des hôpitaux, 1897, lxx, 1141 (bibl.); *Pearson* and *Ravenel*, University Med. Mag., 1900, xiii, 391; and *Sayer*, Pneumonomykosis aspergillina, Jena, 1900.

occasionally dwellers in the human body and appear to be but rarely the cause of disease, passing, rather, a saprophytic existence on dead material in parts of the body which are in communication with the air. Thus they may be found growing on accumulations in the external auditory canal, in dead tissue in the lungs, on walls of cavities, dilated bronchi, etc. Many cases have been reported, however, in which the moulds, especially aspergillus, have been the apparent excitants of serious lesions in men and animals.[1]

Sporotrichosis.—An interesting group of fungi inciting lesions in man was discovered by Schenck[2] in 1898, was later studied by Hektoen and Perkins,[3] and has recently been more fully described by de Beurmann and Gougerot.[4] The disease induced by these parasites had usually been confused with syphilis or tuberculosis until examination of sections and isolation of moulds from the lesions showed that they were due to a group of organisms differing slightly from each other in their cultural and morphological peculiarities. These organisms have been named for their discoverers, Sporotrichum Schencki, Sporotrichum Beurmanni, Sporotrichum Jeanselmei, and Sporotrichum Gougeroti. Whether all these represent distinct organisms is still a matter of discussion.[5] The lesions which they induce are chronic, often ulcerating granulomata. Large abscesses with secondary lymphangitis may occur, and the bones and synovia are occasionally involved. Cases of pyelonephritis, of generalized infection, and of bronchopneumonia due to the fungus have been described. Three deaths are on record. The clinical diagnosis is not difficult to one who is familiar with the disease, but it is usually necessary to make sections or culturcs from the lesions. In sections the characteristic oval spores may be found, either free or in connection with the mycelium or in phagocytic tissue cells. The fungus grows abundantly at room temperatures on Sabouraud's medium, which is composed of water, 1,000 g.; peptone, 10 g.; glucose, 40 g.; agar, 18 g. When the mould is removed from the medium and examined it is found to be composed of a branching mycelium with oval or pear-shaped spores attached in continuity or forming lobulated masses at the ends of the mycelial threads.

Methods of Studying Yeasts and Moulds.

The yeast organisms are in general stained and cultivated by the same methods as those used in studying the bacteria. By treating unstained sections of tissue containing them with a solution of caustic potash the organisms may often be readily demonstrated.

The higher moulds may be simply teased and studied in glycerin or in glycerin and water. They may be stained with alkaline-methylene-blue solution Loeffler's solu-

[1] For résumé and bibl. of relationship of yeasts and moulds to human diseases consult *Ricker, G.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, i, 892. See also *Hektoen, L.*, and *Perkins, C. F.*, Jour. Exper. Med., 1900, v, 77; *Plaut, H. C.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 1; *Buschke, A.*, ibid., p. 155; *Gougerot, H.*, ibid., p. 211.

[2] *Schenck*, Bull. Johns Hopkins Hosp., 1898, ix, 286.

[3] *Hektoen* and *Perkins*, Jour. Exper. Med., 1900, v, 77.

[4] *de Beurmann* and *Gougerot*, Traité des sporotrichoses, Paris, 1912. See also *Hamburger, W. W.*, Jour. Am. Med. Assn., 1912, lix, 1590; *Taylor, K.*, ibid., 1913, lx, 1142; *Meyer*, ibid., 1915, lxv, 579 (bibl.); and *McLean*, ibid., 1917, lxix, 1774.

[5] *Meyer* and *Aird*, Jour. Infect. Dis., 1915, xvi, 399.

tion). When spores have formed in considerable numbers on the more complex forms of moulds, these are not easily wetted by the usual staining fluids, because the air clings so closely among the spore masses. In a mixture of four parts of alcohol and one of aqueous solution of ammonia they are instantly wetted, and may then, with or without staining, be teased and mounted in glycerin. In studying the moulds in the above-described skin diseases it is well, when crust-like masses are to be teased apart, to allow them first to soak for a few minutes in a 5 per cent. solution of caustic potash. In this solution they may be studied, or they may be teased and mounted in glycerin for preservation. Most of the more common moulds are readily grown on the ordinary culture media.

CHAPTER VIII.

THE RELATIONS OF MICROORGANISMS TO DISEASE—INFECTION AND IMMUNITY.

THE PRESENCE OF BACTERIA AND OTHER MICROORGANISMS IN THE BODY: ITS PROTECTIVE MECHANISM.

The Presence of Bacteria.—Bacteria are invariably present in greater or less numbers in the mouth, nose, upper air passages, gastrointestinal and genitourinary tracts of men and animals.[1] Into these places they are more or less constantly brought by the respired air,[2] by food and drink, and in other ways. They are always abundant upon the skin and about the hairs, and the sweat and sebaceous glands. But common and often abundant as are these germs upon the external and internal surfaces of the body, they do not often pass through the healthy mucous or cutaneous surfaces,[3] so that under normal conditions the tissues, the viscera, and the circulating fluids are practically sterile.

Except for certain pathogenic forms which may, under unsanitary conditions, have been set free and transported from men or animals suffering from infectious disease, the bacteria upon the cutaneous or mucous surfaces of the body are for the most part harmless; while certain intestinal forms may even be useful, though not necessary, in promoting digestion. Such symbiotic relationship may continue uninterrupted throughout life unless some injury offers a portal of entry or the reduction of the natural resistance permits stray organisms, which have penetrated the natural boundaries, to obtain a foothold.

The Safeguards of the Body.—The body is guarded in various ways from the incursions of pathogenic and other bacteria, which may be commonly present or only occasionally lodged upon its surfaces. Among the protective agencies of the body may be mentioned the firm, dense skin which while intact protects the interior from the entrance of almost all known microorganisms; the epithelial investment of the mucous membranes, in several places swept by cilia; the protected situation of most of the mucous surfaces, the germicidal qualities of some of the secretions, such as the saliva, gastric juice, mucus, etc.[4]

[1] For a summary of facts concerning the bacterial flora of the body surfaces consult *Welch*, Surgical Bacteriology, System of Surgery; see also *Ford*, Trans. Assoc. Amer. Phys., 1900, xv, 389 (bibl.); and *Selter*, Ztschr. f. Hyg., 1906, liv, 363.

[2] For a résumé of microorganisms in the air see *Gottstein, A.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1897, iv, 87; also *Firth*, Studies from the Department of Pathology, Col. Phys. and Surg., Columbia University, 1899–1900, vii; and *Chapin, C. V.*, Jour. Am. Med. Assn., 1914, lxii, 423

[3] It should be remembered that the gastrointestinal canal, the lungs, and other viscera which are in communication with the exterior, although within the limits of the body, still form, strictly speaking, its outside, in distinction from the intimate recesses of the tissues in which the life processes go on.

[4] For a résumé of the protective action of the skin, mucous membranes, etc., see *Metchnikoff*, Immunity in Infective Diseases, 1905.

See for summary of protective agencies of the lungs, p. 684. For a study of the action of saliva on bacteria see *Clairmont, P.*, Wien. klin. Wchnschr., 1906, xix, 1397 (bibl.). For bactericidal action of mucus see *Arloing*, Jour. de phys. et de path. gén., 1902, iv, 291 (bibl.).

The Portals of Entry.—But notwithstanding the safeguards of the body against the access of microorganisms, these do frequently enter; this may occur in severe injuries to the skin or mucous membranes or through very slight and unnoticed abrasions or other solutions of continuity. Entrance may be gained to the tissues through the minute ducts of the sebaceous or sweat glands; from the mouth, tonsils, gastrointestinal canal,[1] and the respiratory passages and surfaces, either with or without obvious injuries to the investing epithelia. The rôle of insects in the conveyance of infectious agents is of great importance.[2] Microorganisms may enter the body during intrauterine life.[3]

There is abundant evidence that even in health, through the pharynx, tonsils, and intestines, a small number of bacteria frequently enter the recesses of the body, but are safely disposed of through the protective mechanism presently to be considered. So that while we may, as above stated, consider the interior of the healthy body as *practically* sterile, it is still possible by careful and discreet searching to discover here and there bacterial detritus and bacteria on their way to destruction.[4]

The Protective Mechanism.—When in one way or another bacteria or other germs have entered the tissues, they may encounter a series of obstacles to their spread or continuance as well as to their proliferation there, even should the general nutritive conditions be favorable. In the first place the lymph-nodes filter out of the tissue fluids microorganisms which have entered them, holding them back from the general circulation or destroying them.[5] The power of certain of the body fluids and of living cells—phagocytes—under favorable conditions to kill and dispose of germs, is of great importance and will be referred to again.[6] The elimination of microorganisms from the body through its secretions,[7] such as urine, bile, milk, sweat, saliva, etc., is a matter of great significance, but one upon which the scope of this book does not permit us to enter.[8]

[1] For bibliography concerning the permeability of the gastrointestinal canal for bacteria refer to p. 785.

[2] *Nuttall*, Johns Hopkins Hosp. Rep., 1900, viii, 1. For a résumé with bibl. of the transmission of infective material by flies and other insects see *Chapin*, Sources and Modes of Infection, 2d ed., New York, 1912; also *Graham-Smith*, Flies in Relation to Disease, Cambridge, 1913; for study of economic loss by insects see *Howard*, U. S. Dept. Agricult., Bureau of Entomology, Bull. 78, 1909.

[3] For a résumé of studies on the congenital transmission of infectious agents see *Wassermann* and *Keysser*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, i, 659 (bibl.); also, *Balantyne*, Antenatal Pathology, 1902; and *Lynch*, Bull. Johns Hopkins Hosp., 1902, x, 283.

[4] *Adami, J. G.*, Jour. Am. Med. Assn., 1899, xxxiii, 1509, 1572; and Brit. Med. Jour., 1914, i, 177; and *Wrzosek, A.*, Virchows Arch., 1904, clxxviii, 82; see also for an experimental study of the disappearance of bacteria from the blood, *Schwarz*, Ztschr. f. Heilk., Abth. f. Path. Anat., 1905, xxvi, 295.

[5] *Manfredi, L*, Virchows Arch., 1899, clv, 335, for a study of the germicidal and other action of lymph-nodes; also *Bezancon* and *Labbé*, Arch. de méd. expér., 1898, x, 389.

[6] For studies of the capacity of the living body to dispose of bacteria when these are injected into the blood, see *Werigo*, Ann. Inst. Pasteur, 1894, viii, 1; also *Bail*, Arch. f. Hyg., 1905, lii, 272; and *Buxton* and *Torrey*, Jour. Med. Research, 1906, N. S. x, 5.

[7] Consult *Sherrington, C. S.*, Jour. Path. and Bacteriol., 1893, i, 258; *Biedl* and *Kraus*, Arch. f. exper. Path., 1895, xxxvii, 1 (bibl.); *Hintze* and *Lubarsch*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, i[1], 287. For study of disappearance of bacteria from the body, see *Pawlowsky*, Ztschr. f. Hyg. u. Infectionskrankh., 1900, xxxiii, 261; also *Asch*, Centralbl. f. d. Krankh. d. Harn- u. Sex.-Org., 1902, xiii, 249, 324.

[8] For a suggestive summary of the various factors which are or may be concerned in the protection of the body against the invasion and action of microorganisms, see *Meltzer*, Trans. Cong. Am. Phys. and Surg., 1900, v, 12; see also ref. to *Wassermann* above.

See also for the importance of a lesion in animal tissues for the lodgment and multiplication of bacteria within it, *Cheesman* and *Meltzer*, Jour. Exper. Med., 1898, iii, 533; and *Brewer, G. E.*, on

ACTION OF BACTERIA AND THEIR PRODUCTS IN THE BODY.

The Bacteria.—When bacteria do enter and grow in the body, the cells and tissues near them may show very marked alterations, due to their influence. The cells may be swollen, or their nuclei may disappear, and the protoplasm may be converted into hyaline material or into a mass of transparent or coarsely granular particles, or may completely disintegrate. The intercellular substance near the bacteria may also soften and disintegrate. In a word, the tissue in their immediate vicinity is often found in a condition of necrosis of one kind or another. The walls of blood-vessels near which they lie may be damaged and the blood which these carry may form thrombi. The bacteria may themselves enter the vessels and proliferate in the blood; they may be swept away as emboli to remote parts of the body (Fig. 61, page 109), and establish new foci of bacterial proliferation and tissue necrosis—*septicemia.*

Some bacteria, instead of inducing a simple necrosis, incite at the same time, as we have already seen, a more or less intense inflammation (Fig. 62, page 110). This inflammation may be of a simple productive form, similar in its effects to that incited by the presence of any irritating foreign body; or it may be active, progressive, and exudative in character; or the bacteria may determine, in some way as yet unknown to us, very peculiar and characteristic inflammatory changes, which result in the formation of new tissues of various kinds (see Tuberculosis). Some forms of bacteria find in the blood, others in the tissue spaces and lymph-vessels, the conditions most favorable for their proliferation. Others seem to select certain sites for their activities; for example, the Streptococcus viridans usually attacks the heart valves; the pneumococcus, the cornea and the lungs.

Bacterial Poisons.—But the presence of microorganisms themselves is not indispensable for the incitement of either local or general pathological processes. These may be induced by various chemical products eliminated or stored up in their protoplasm by the metabolism of the germs. These deleterious bacterial products may, as we have already seen, be those substances called *toxins,* or they may be albuminoid substances—*toxalbumins* or *toxalbumoses.* Stored up in the protoplasm of the germs themselves, this poisonous material has been called *bacterioprotein* and *endotoxin.*

It seems probable that the toxic effects of some bacteria may be due not to their immediate product but to the action of bacterial enzymes, whose effects upon certain body proteins result in the development of the toxic albumoses which are the active damaging factors.[1]

unilateral infection of the kidney following injury, Surg., Gynec., and Obst., 1906, ii, 485; also on the significance of granulation tissue in wound infection, *Afanassieff,* Zieglers Beitr., 1897, xxii, 11; *Cobbett* and *Melsome,* Centralbl. f. allg. Path. u. path. Anat., 1898, ix, 827 (bibl.); and *Jürgelünas, A.,* Zieglers Beitr., 1901, xxix, 92 (bibl.). For the rôle of the spleen in infection and intoxication see *Courmont* and *Duffau,* Arch. de méd. expér., 1898, x, 431, *Nicolas* and *Beau,* Jour. de physiol. et path., 1909, iii, 68; *Morris, D. H.,* and *Bullock, F. D.,* Ann. Surg., 1919, lxx, 513.

[1] Much of the literature on this subject has been brought together by *Vaughan* and *Novy,* Cellular Toxins, 4th ed., Philadelphia, 1902. See also *Vaughan,* Protein Split Products in Relation to Immunity and Disease, New York, 1913. The general chemical relationship of bacterial products to other organic compounds is set forth in *Wells,* Chemical Pathology 4th ed., Philadelphia, 1920, p. 101; see also *Pick. E. P.,* Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, i, 685.

Thus, it has been found that the maceration of blood serum for a few hours with dead bacteria or trypanosomes, with minute quantities of agar or peptones, or even with insoluble materials such as kaolin or barium sulphate, produces in the serum a toxic body capable of causing anaphylactic shock.[1] Such a body must exist in the blood in a highly labile condition, since it is influenced by substances whose functions must be exhibited solely in their colloidal condition. That such colloidal states may be of importance is shown by the fact that an intravenous injection of a freshly prepared aqueous solution of a dye, Bordeaux red, is harmless, but that if the colloidal state of the solution is altered by boiling for a short time or by standing for a few hours, almost instantaneous death of the animal results from the injection. This effect seems due to intravascular clotting. The toxic powers of bacteria may be due, therefore, in some instances, not to specific toxins produced from their bodies, but merely to alteration in the condition of an otherwise harmless protein of the normal blood serum.

A similar change may lie at the root of a phenomenon discovered by Bail, who found that when one injects into animals sterilized exudates induced by the action of various pathogenic microorganisms—tubercle, typhoid, and dysentery bacilli, pneumococcus, staphylococcus, etc.—together with sublethal doses of cultures of the organisms themselves, the death of the animal is brought about much sooner than when the bacteria alone are introduced. Bail, as the result of many experiments, assumes that under these conditions the exudate contains substances which foster the deleterious effects of the living organisms by interfering in some way with the protective agencies of the body. These hypothetical substances he has called *aggressins*, and he believes them to be formed by the bacteria as they grow in the body.[2] This aggressin theory has not found general acceptance and much experimental evidence has been brought forward to controvert it.[3]

Intoxication—Toxemia.—Some of the poisons act locally at or near the seat of their manufacture by the growing germs. Others gain access to the body at large and are widely distributed, inducing what may be called the phenomena of septic *intoxication—toxemia.*

The phenomena of septic intoxication may be induced by the products of bacterial growth outside of the body when these in considerable quantity are in any way taken into it. This is true not only of poisons elaborated outside the body by pathogenic bacteria, but also of many forms of bacteria usually harmless. Thus are caused many kinds of food poisoning which simulate but are not actually infectious diseases, because there is no development within the body of the disease-inciting germs.

Similar local and general effects may be induced in the body by other poisons than those of bacterial origin. Ricin and abrin, for example, well-known vegetable poisons, and the venom of scorpions and of certain

[1] *Novy, F. G.*, and *DeKruif, P. H.*, Jour. Am. Med. Assn., 1917, lxviii, 1524.

[2] For a discussion of the so-called aggressins see *Bail* and *Weil*, Centralbl. f. Bakteriol., Orig. I, 1906, xlii, 51, 139, 241, 335, 437, and 433.

[3] See *Sauerbeck*, Ztschr. f. Hyg. u. Infectionskrankh., 1907, lvi, 81.

snakes are closely similar in their action to the toxins which the bacteria form either within or without the body.

It should be remembered in this connection that effects closely resembling those due to bacterial or allied poison may be induced by toxic agents developed within the body as a result of defective elimination or faulty cell metabolism—*autointoxication.*

Thus the deleterious effects of pathogenic bacteria upon the body are but in small measure simply mechanical. Local necrosis and inflammation, albuminous degeneration of cells, leucocytosis and[1] other alterations of the blood, fever, structural lesions and functional disturbances in the nervous system, irregularities in the circulatory and respiratory mechanisms, hemolysis and agglutination of the red blood-cells, and thrombosis,[2] etc., may follow the distribution in the body of bacterial toxins,[3] a good example of which is the extract of tubercle bacilli known as tuberculin.

PROOFS OF THE INFECTIVE NATURE OF BACTERIA FOUND IN THE BODY

It will be seen, from what has now been said of the bacteria, that in different parts of the system in health, and in a large number of abnormal conditions, various forms of bacteria occur; but it is quite evident that the significance which we must attach to their mere presence varies greatly. In a large number of cases, especially when on parts exposed to the air or in the gastrointestinal canal, they are evidently of no more importance than so much inorganic dust. When, however, special forms of bacteria are uniformly present in connection with well-defined diseases, or in their lesions, and especially if these largely preponderate, the conjecture is certainly justified that the microorganisms may have something to do with their incitement. Yet in all such cases we have to consider the possibility that it is the abnormal state of the body or the character of a lesion, brought about perhaps in other ways, which affords conditions suitable for the growth of this form of bacteria, and that these may consequently be present in considerable numbers, while in the absence of such conditions they would be unable to develop. Even the constant presence in the body, in certain diseases, of bacteria which evidently produce well-marked local effects, either inflammatory or degenerative, does not absolutely prove their etiological relationship to the disease, although it renders it in a high degree probable.

It is desirable in every case in which the evidence of the etiological relationship of a specific microorganism to a disease is to be set forth, that we should be able to demonstrate the constant presence in the body of the special form of microorganism during some period of the disease, obtain this by culture in a pure condition unmixed with any other living thing or with any chemical substance not belonging to it, and finally, by the introduction of the purified organisms into a healthy animal, be able

[1] See *Flexner*, Johns Hopkins Hosp. Rep., 1897, vi, 259.

[2] For bacterial hemolysins see *Pribram*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, ii, 1328.

[3] On the theory of bacterial infection, see *Radziewsky*, Ztschr. f. Hyg. u. Infectionskrankh., 1901, xxxvii, 1.

to induce the disease in some definite form. When all this is done, and not before, can we assert that the evidence establishing the causative relationship between a given form of bacteria and any special infectious disease, is entirely at our command.

But the fulfilment of these strict logical requirements is very difficult in many cases, and in some, apparently, almost if not quite impossible; for we must remember, in the first place, that the lower animals, upon which alone, for the most part, inoculation experiments are practicable, are apparently not subject to certain important diseases of man; and, second, that they present among themselves the most marked differences in the degree and manner in which they are affected by inoculation with pathogenic bacteria. Desirable as is the complete fulfilment of the above requirements in every case, it must be admitted that a reasonable certainty regarding the bacterial origin of a given disease may sometimes be arrived at without positive results from the inoculation of the bacteria associated with its lesions. The agglutination test and the tests for specific lytic substances or opsonins applied under proper conditions may afford valuable evidence of the nature of an infection (see pages 219 and 228).

The complete demonstration which is desirable has as yet been furnished in but a moderate number of diseases. In many others, however, enough has been done in the way of study and experimentation to render it altogether certain that they are infectious and to establish beyond reasonable doubt the identity of the microorganism or microorganisms involved.

CONDITIONS INFLUENCING THE OCCURRENCE OF INFECTIOUS DISEASES.

Conditions of the Body.—It has been learned as a result of a great deal of observation and experiment, that although certain diseases are always associated with the presence and growth in the body of particular species of microorganisms, there are still various other accessory factors which have an important bearing upon the inception and course of the diseases. Thus, while the presence in the body of a particular species of microorganism is the most significant and fundamental of the determining agencies in the infectious diseases, the numbers in which they are present—*i.e.*, the size of the dose—and the varying virulence which the same species under different conditions possesses, as well as the varying capacity of resistance to the incursions of the germs which the body-cells at different times and under differing conditions exhibit, are all factors of the greatest moment.

Malnutrition, mental or physical overwork, injuries, bad hygienic surroundings, the abuse of alcohol and other forms of intemperance, as well as many other conditions which lead to deterioration in the general health, are often decisive factors in determining the intensity or even the occurrence of the diseases due to bacterial incitement. It is thus clear that the action of a given germ in the living body depends only in part upon its intrinsic capacities—which in themselves are very variable—but also and in marked degree upon the capacities, also variable,

which exist at the moment in the body-cells among which the lot of the germs is cast.

It should be always borne in mind that the human body is a great aggregate of groups of coordinated cells which, under normal conditions, all act in harmony for the maintenance of the life and functions of the individual. The cells and cell communities in health not only do this, but they have the power of resisting and to a certain extent overcoming various deleterious agencies to which the body is more or less constantly liable.

What we call hereditary or acquired predisposition to an infectious disease, such as tuberculosis, for example, is simply a lack of the usual capacity of the cells of the body—whether through a structural or physiological fault we do not yet know—to cope with—that is successfully to adapt themselves to—the destructive tendencies of the living microorganisms when once these gain a foothold in the body.

Conditions of the Microorganisms.—On the other hand, the varying potencies of the bacterial species concerned in a given infection, which are linked especially to their toxins, and the influence of environment upon these, exalting or reducing them, as the germs adapt themselves to antagonistic or to congenial hosts; the origin of the strains and the numbers involved—these are all factors in virulence of supreme importance; but our space does not permit us to consider them further here.

We thus see that, in studying the conditions under which infectious diseases occur, the work is by no means complete when the bacterial species which incites the disease has been discovered, but that then the more obscure determining and influencing agencies must be worked out in each case.[1]

Infection and Immunity.

INFECTIOUS DISEASE AND THE NATURE OF INFECTION.

Infectious diseases are those which are incited by the entrance into the body and proliferation there of pathogenic microorganisms. *Infection* is the act or process by which such diseases are incited. The process of infection is "the interaction between the organism and the microorganism."

In the more exact usage of the words "infectious" and "infection" which our new knowledge demands, it is customary and convenient to limit the term "microorganism" to the fungi—bacteria, yeasts, and moulds—and to the protozoa representing the animal kingdom, excluding altogether the entozoa and other animal parasites.[2]

The modern conception of infection implies the presence in the body of the *living* microorganisms themselves; that is, of something capable of multiplication, or at least of reproduction and development, and not

[1] For a résumé of the nature and conditions of infection, see *Wassermann* and *Keysser*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, i, 555 (bibl.); for a study of the general reaction of the body in infection, see *Blumenthal*, ibid., 1st ed., i, 326.

[2] With this somewhat arbitrary limitation, neither trichinosis nor scabies, for example, would be considered an infectious disease, although they are often, for the lack of a distinctive word, thus designated. *Infestious* and *infestion* are not infrequently employed for animal parasites.

alone of the poisons which they may and usually do produce. It is customary to look upon the effects of the absorbed poison which microorganisms furnish as *intoxications*, whether these poisons be formed inside the body in infectious diseases and in other conditions, or outside of it and subsequently introduced. That condition in which there is evidence of wide distribution of pathogenic microorganisms and their products in the blood is called *septicemia* (page 238).

It is evident from what has been said that infectious disease cannot exist without the presence in the body of microorganisms. But, on the other hand, microorganisms can and do frequently exist in the body without the incitement of infectious disease. Whether a microorganism be pathogenic or not depends upon the variable susceptibilities of the host as well as upon its own—also variable—nature and qualities. No microorganism is intrinsically pathogenic; the very conception implies a relationship. This obvious fact is overlooked by those who see in the microorganisms alone the essential specific features of infectious diseases; who would classify these diseases exclusively by the nature of their excitants, and who look upon the latter as the true "causes" of the phenomena through which disease is manifested (page 8).

INCUBATION PERIOD.

It is characteristic of infection that a certain time elapses between the entrance of the infective agent and the manifestation of symptoms or the development of lesions. This interval is called the "incubation period" of the infection and varies with different infective organisms. This incubation period is that time during which the microorganisms are increasing sufficiently in number or virulence in the body to induce symptoms and lesions or are passing through developmental cycles marking their adaptation to the environment furnished by the host. During this incubation period the body may become very sensitive to a renewed infection with the same organism, and may show such sensitization in various ways. Thus, a quiescent tuberculosis renders the whole organism reactive to an injection of tubercle-bacillus toxin, while the sensitization of the skin affords a convenient diagnostic reaction, which bears the name of v. Pirquet.[1]

FORMS OF INFECTION.

Mixed or Concurrent Infection.—It should be borne in mind that the body which is already the seat of an infectious disease is usually especially susceptible to the action of other pathogenic germs, should these once gain entrance; and also that the lesions which are associated with many of the infectious maladies afford portals of entry through the skin or mucous membranes to other microorganisms, against the entrance of which the healthy body opposes most efficient barriers. In fact, we now know that the action of two or more pathogenic microorganisms in the body at the same time is of very frequent occurrence, many of the

[1] *v. Pirquet*, Die Serumkrankheit, Vienna, 1905.

so-called complications of the infectious diseases being due to secondary infection with a new germ species. Numerous examples of this "mixed" or, better, "concurrent," infection are noticed in other parts of this book.[1]

Many important facts have been revealed by the study of bacterial association in cultures as well as in infectious diseases of men and animals which cannot here be considered.[2] It may be said in general that in animals as in man concurrent infection with a second microorganism increases the gravity of the original situation. On the other hand, certain experiments seem to indicate that sometimes the concurrent action of a second germ—streptococcus, for example, with the anthrax bacillus —may render a virulent organism comparatively innocuous. But the conditions of the experiments are in either case so complex that the full significance of many curious phenomena is not yet apparent.

Congenital Infection.—Infection of the fetus through such lesions of the placenta as permit of the passage of pathogenic microorganisms from the blood of the mother to that of the child is of occasional, but not frequent, occurrence. While the barriers against such transmissions are, under normal conditions, effective, disturbance in the placental circulation, lesions of the vessel walls or of the tissues and covering of the chorionic villi favor it. But infection may occur without demonstrable evidence of such lesions. Thus fetal infection is known to have occurred in various phases of suppurative inflammation, in tuberculosis, typhoid fever, anthrax, syphilis, the exanthematous fevers, etc. There is considerable evidence that rarely the tubercle bacillus may be transmitted from mother to offspring, and remaining for a time inactive may later induce the characteristic lesions.[3]

Terminal Infection.—The victims of chronic disease of the heart, blood-vessels, kidneys, liver, etc., are particularly susceptible to the incursions of pathogenic microorganisms and to infectious diseases of one kind or another. Such persons, with or without definite lesions, are in fact liable finally to succumb to the complicating disease. The phrase "*terminal infection*" has been applied by Osler and others to this concurrence of diseases of such different nature, in which the chance infection of a vulnerable organism is so apt to prove fatal.[4]

Great care is, however, necessary in determining the significance of the various forms of bacteria which may be present in the body after death. Not only may bacteria develop to a considerable extent in the body during the hours which precede death when the natural protective agencies are halting or abeyant, but this may occur without such a reaction on the part of the body-cells as is necessary to constitute an actual infection. Furthermore, multiplication and distribution of bac-

[1] For bibliography of mixed infection see *Bernheim* and *Gruber*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1895, ii, 1; also *Wassermann* and *Keysser*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, i, 632.

[2] Consult *Th. Smith*, Trans. Assn. Am. Phys., 1894, ix, 85: also *Moore*, Pathology and Differentia Diagnosis of Infectious Diseases of Animals, 1906.

[3] For bibliography and summary of fetal infection, see *Lubarsch*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, i[1], 427; also *Fischl*, in Grancher, Comby, and Marfan, Traité des Maladies de l'Enfance, Paris, 1904, i, 454 (bibl.).

[4] For a study of this class of cases, see *Flexner*, Trans. Assn. Am. Phys., 1896, xi, 229.

teria in the body after death is of frequent occurrence and must in every case be taken account of in weighing the evidence for terminal infection.

COMMUNICABILITY OF INFECTIOUS DISEASES.

It is important in practical dealings with the infectious diseases to consider them in the light of the relative liability of transmission of the actually known or assumed microorganisms from diseased to healthy individuals.[1]

In the first place, it should be borne in mind that the lower animals are insusceptible to the ravages of some of the microorganisms which readily incite infectious disease in man. Thus the lower animals with the exception of the primates and the rabbit are, so far as we know, naturally immune to syphilis. To certain diseases of the lower animals, on the other hand, man is not subject. But to certain other infectious diseases, tuberculosis for example, both men and lower animals are susceptible, and both are, in fact, under the prevailing conditions of modern life, frequent victims.

So far as the liability to the transmission of the infectious agents from man to man is concerned, there is a very marked and significant difference between the infectious diseases. It is common usage to speak of the transmission or communication of disease, as if disease were a self-existent thing. This usage fosters much loose thinking. What we call disease is a process involving a departure from, failure in, or perversion of normal physiological action, either in the material constitution or in the functional integrity of the living organism. When, therefore, we speak of the transmission or communication of disease, what we really mean is not that the disease, but the agent capable under suitable conditions of inciting the disease, is transmitted or communicated. If we hold this obvious implication in mind, it is useful to group the infectious diseases of man into two great primary classes: 1st, *Those which under the usual conditions of life are not readily communicable.* 2d, *Those which under the usual conditions of life are readily communicable.*

But while, for convenience, we may speak of *non-communicable* and *communicable infectious* diseases, we should remember that these two classes merge into each other, and that in fact the agents of infection may at least artificially in all cases be conveyed from one individual to another. It is only when the conveyance under natural conditions occurs in a round-about way, or through intermediary agencies, such as the mosquito for example, in malaria or yellow fever, that one may advisedly speak of non-communicable infectious diseases.

Among the communicable infectious diseases there exists the widest difference in the liability to transmission under ordinary circumstances. Thus the infectious agents in measles are given off from the body under such conditions as render possible and frequent their direct transmission to another individual without the obvious contacts of person or discharges with which the conveyance of infective agents is associated in most of the

[1] See *Chapin*, Sources and Modes of Infection, 2d ed., New York, 1912.

communicable diseases. In syphilis, tetanus, and rabies, on the other hand, transmission of the infectious material is rare or impossible without a direct inoculation.

Between these extremes the widest diversity exists in the liability to transmission of the infectious agents of the diseases of this class. In fact the liability to infection on the part of a healthy individual in the presence of a victim of infectious disease is largely dependent upon the intelligent care which is exercised in the disposition of the material containing the pathogenic microorganism, usually secretions or excretions, which in one way or another the infected body sets free.

So that while it may be useful to arrange the communicable infectious diseases in groups, or in such serial order as may indicate the degree of communicability of each under the ordinary conditions of life, it should always be borne in mind that this classification is not fundamental, as is that by which the infectious diseases as a whole are set apart from other diseases, but is closely dependent upon the sanitary conditions under which each case may be placed. Thus tuberculosis, or diphtheria, or pneumonia may be high on the list as readily communicable if the patient be housed in a crowded tenement with ignorant or careless attendants, while if subjected to the intelligent ministry of sanitary science these diseases may be accounted as relatively slightly communicable.[1]

Communicable infectious diseases sometimes affect a considerable number of persons in a community. This constitutes an *epidemic*, and the term *epidemic disease* is used. So also if an infection is constantly present in a certain locality it is said to be *endemic*. The term *pandemic* is used to indicate the involvement in a particular infectious disease of persons scattered over a large territory.

IMMUNITY.

Nature and Forms of Immunity.

We have seen that *an infectious disease is one incited by the entrance into the body and proliferation there of pathogenic microorganisms, and that infection is the act or process by which such a disease is incited.*

The fact that all animals are not equally susceptible to the ravages of pathogenic microorganisms, and that in man an individual and often a changing predisposition or invulnerability to the incursions of these organisms exists; the further observation that one attack of an infectious disease often protects the victim for a longer or shorter time against a recurrence; finally, the fact that recovery is ever possible when once self-multiplying disease-producing germs have obtained a foothold in the body—all these facts and observations are of such singular import and interest that, especially of late years, there has been much study on the nature of the agencies which the body brings into play in establish-

[1] Before the knowledge of pathogenic microorganisms had become precise, readily communicable diseases were called contagious in a rather loose and ill-defined way, and the unknown excitant was called the *contagium*. The word "contagious" is still used, in various senses, to the detriment of science and should be replaced by the word "communicable" as above indicated.

ing immunity in the face of microbic invasion, and in coping with the various deleterious factors at work when once a foothold is obtained. The scope of this book does not permit us to enter in detail into this most fascinating and important field. We can give only a brief summary of some of the more important features.

Immunity is insusceptibility, or capacity for resistance on the part of the body to disease or, in the more limited sense, to infection or intoxication or their effects.

If we recall the ways in which bacteria damage the organism, it will be evident that immunity may be due to the fact that the microorganisms in question simply do not proliferate in the body, failing, even should they gain entrance, to find the necessary conditions.[1] On the other hand, though the conditions be in general favorable, substances may exist or be formed in the body which destroy the invading germs. In other words these may at once or soon be disposed of by germicidal substances, either in cells or in solution in the body fluids.

Or, the toxic substances which microorganisms set free, as in the process of their nutrition they decompose organic ingredients of the tissues or body fluids, may be rendered inert by further decomposition or combination with substances present or formed in the tissue fluids. Or, furthermore, the cells which are susceptible to the presence of the toxins may become less vulnerable by adaptation to the deleterious effects of the latter.

Immunity from an infectious disease may be **natural** or **hereditary.**[2]

The absolute or relative insusceptibility of turtles and fishes for tetanus, of rats for anthrax, and of many of the lower animals for syphilis and for scarlatina, are examples of hereditary or natural immunity which we need not further consider here. Immunity is variable and rarely absolute, and is subject to individual, as well as racial, variation.

On the other hand, immunity may be **acquired.** Acquired immunity may be secured by an attack of the disease from which the individual has recovered—*natural immunization.* Or, immunity may be acquired by the introduction into the body of some material which gradually diminishes susceptibility without inducing distinct disease—*artificial immunization.* Acquired immunity may be transmitted from parent to offspring.

Most of the infectious diseases appear to confer a certain degree of insusceptibility to subsequent attacks of the same disease, though this may be partial and temporary. The exanthemata afford the most striking examples of acquired immunity after an attack of infectious disease.

Let us now look more closely at some of the ways in which the body may thus protect itself from the consequences of infection.

[1] For a most suggestive and valuable paper on the adaptation of pathogenic bacteria to different species of animals, see *Theobald Smith*, Philadelphia Med. Jour., 1900, v, 1018.

[2] For a study of the theories of natural immunity, see *Müller*, Infection u. Immunität, 1912. For a study, with bibl., of the protective processes in natural immunity, see *Kisskalt*, Ztschr. f. Hyg. u. Infectionskrankh, 1904, xlv, 1, and ibid., 1904, xlvii, 243. For a study of inherited immunity, see *Kleine* and *Möllers*, ibid., 1906, lv, 179.

It is well known that bacteria artificially introduced into the blood of animals may, after a short time, wholly disappear from the circulating fluid, and be found in large numbers in leucocytes and other cells. We have already seen in the study of inflammation (page 118) that certain cells of the body are capable of taking up not only various kinds of alien substances, but also microorganisms which enter the tissues, into their cytoplasm (Fig. 70, page 120) and may there kill and destroy them (Fig. 113). This mode of destruction of microorganisms, largely by leucocytes, but also by other mesodermal cells, which when thus engaged are called phagocytes (page 119), plays a most important part in the establishment of immunity. On the other hand, certain ingredients of the body fluids, formerly called *alexins* or "defensive proteins," acting outside of cells, have been shown to possess marked germicidal

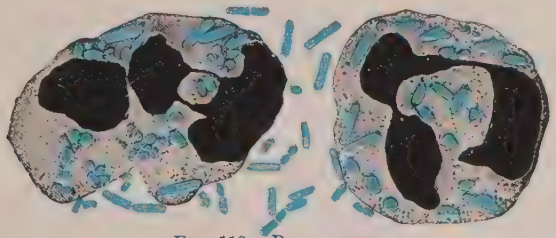


FIG. 113.—PHAGOCYTES.

In fluid from the peritoneal cavity of an immunized guinea-pig a few hours after the introduction of the bacilli of typhoid fever. Degenerative changes are seen in many of the bacteria within the cells.

powers. While thus it might appear that two fairly distinct agencies are of importance in enabling the body to resist the incursions of pathogenic germs—cellular or "phagocytic," and what may be called "humoral" or chemical—it is obvious that whatever destructive power the body possesses toward microorganisms must ultimately be due, directly or indirectly, to cell activities. This phase of immunity has been characterized as *antimicrobic, antibacterial*, or *bacteriolytic immunity*, because it is a mode of protection in which bacteria themselves are destroyed or their growth in the body is limited or prevented.

Not less important is another phase of immunity—*antitoxic immunity*—by which the body protects itself against the toxic substances through which, in many instances, the most serious manifestations of infection occur.

These two forms of immunity—antitoxic and antibacterial or bacteriolytic—will be considered in detail in a following section.

Furthermore, the microbic toxins which are set free by the microorganisms, like other poisons, may be eliminated together with the waste products of body metabolism through the kidneys, skin, etc.

ARTIFICIAL IMMUNIZATION.

General Methods and Principles of Artificial Immunization.—It was not possible to gain a clear conception of the factors entering into the complex problems of immunity until animal experimentation had

revealed a host of significant facts bearing directly upon questions which for a long time had seemed insoluble. It has been found as the result of experimental researches that artificial immunity can be secured by gradually rendering the body tolerant to the presence of the infective or toxic agencies without actually inciting the characteristic specific disease.

I. In one class of procedures artificial immunity is secured directly or indirectly through the action in the body of bacteria or other microbes or microbic poisons whose virulence has been in one way or another reduced but not rendered altogether inert; or by the action on relatively insusceptible animals of microbes or microbic poisons of unimpaired virulence. Immunity induced in this way as the result of direct adaptation of the body cells to the new conditions is called ACTIVE IMMUNITY.

1. Active immunity to particular forms of infectious disease may be conferred by inoculation *with cultures of the germ inciting the infection whose virulence has been artificially reduced—attenuated cultures.* This reduction of virulence may be accomplished in various ways: by cultivation at temperatures above their optimum; by successive inoculations into insusceptible animals; by prolonged artificial cultivation in the presence of oxygen; by exposure to certain inorganic chemical substances, as the diphtheria bacillus to trichloride of iodine, anthrax to bichromate of potash, etc.; by exposure of cultures to organic extracts or products of animal or vegetable cell metabolism; by drying (hydrophobia), or by exposure to sunlight; by killing the germs by heat or by ether, using for injection emulsions of their dead bodies containing the so-called endotoxin; and in other ways.

With the virulence of the microorganisms reduced in varying degrees in one or other of the ways just mentioned, the gradual habituation of the bodies of animals to the presence of pathogenic germs may be pursued until cultures of full virulence are tolerated.[1]

2. Active immunity may be conferred by the injection, in gradually increasing doses, of the *metabolic products of bacterial growth,* either with or without the dead bodies of the germs themselves—the bacilli of typhoid fever, for example. The primary virulence of these usually toxic products of microbic growth may be in various ways diminished, by heating, by mixing with organic extracts such as that of the thymus gland, or with an inorganic chemical substance such as trichloride of iodine, or by small doses of the already prepared antitoxin—see below.

3. Active immunity may be secured in some cases by the inoculation of animals, which are but moderately susceptible to the species employed, with small but increasing quantities of *germs having unimpaired virulence.* Under these conditions the animal becomes less and less responsive to the germ, until finally it may display no reaction after a quantity of the virulent culture which at first would have been inevitably fatal. In man the use of the so-called sensitized vaccines has produced valuable results. Live bacteria are macerated with an excess of antiserum, and the combination is injected.

4. Immunization in man by the direct use of dead bacteria or bacterial poisons or of virus of diminished virulence has been largely practised in typhoid fever, cholera, and hydrophobia.

In active immunity the protective material is elaborated by the immunized individual, the process requires considerable time, and the

[1] On the contrary the virulence of a particular strain of pathogenic bacteria may be exalted by a series of "passages" through a susceptible animal. When the infection from inoculation has developed in the first animal, cultures derived from it are used to infect a second, and so on through a series of "passages."

In this way, it is assumed, the self-protective adaptations of the bacteria are made evident in the increasing potency of the toxins which they produce, the toxins being one of the important factors in injuring the protective mechanism of the host.

effect lasts for a considerable period. The recent developments in scientific practice seem to point to the fact that in many instances an attack on the toxins of the bacteria is not the way of ultimate success. The real object is to destroy the invader and the only advantage in neutralizing the toxin is the protection of the cells of the organism from serious injury while they are preparing to carry out this destruction.

The beneficial effects ascribed to the injection of bacterial cultures killed by heat have been recently shown to be due in many instances to mere non-specific stimulation of the hematopoietic system, in which antibodies are produced, together with a mobilization of the serum ferments,[1] and not to any specific bacterial protein. Thus, the beneficial results noted clinically in typhoid fever after injections of large numbers of killed typhoid bacilli could be duplicated by injections of a proteose.

II. *In a second class of procedures artificial immunity is secured by the direct mingling of the body fluids from an individual already immunized in some of the above ways, with those of the individual to be protected. Immunity secured in this way, in which the immunizing substance used has been elaborated by another individual, is called* PASSIVE IMMUNITY.

1. *Extracts of various organs and tissues* of animals suffering from infectious disease rendered germ-free and injected into healthy animals, have been found in some cases to confer a certain degree of immunity.

2. The *blood serum of animals naturally immune* to a particular infectious disease has been found, on injection into those which are susceptible to the same disease, to impart in some cases a certain degree of insusceptibility.

3. The *blood serum,* finally, *of animals* which have been rendered in one way or another *artificially immune* to certain diseases, if introduced under proper conditions into another susceptible animal, has been found not only to confer a temporary immunity, but, if administered to an already stricken individual, to aid him in the most marked and efficient way to overcome the deleterious agencies at work.

The use of blood serum of artificially immunized animals for this purpose is of far greater practical importance than either of the methods 1 or 2.

In passive immunity the protective material is furnished ready made, the effect is secured at once and is temporary.

Antitoxic Immunity.

It appears from a study of the results of artificial immunization, as well as of the immunity which is involved in the natural recovery from infectious disease, that one of the ways in which immunity is secured is by the formation of substances in the body fluids which in some way neutralize or suspend the action of toxins—**antitoxic immunity.**

Thus in diphtheria and tetanus the antitoxic substances are largely developed, while in many other infectious diseases, such as cholera and typhoid fever, it appears to be, in part at least, through the bacteriolytic substances that protection is secured. While in many instances

[1] *Jobling* and *Petersen,* Jour. Am. Med. Assn., 1916, lxvi, 1753; *Miller*; and *Lusk,* ibid., p. 1756; *Miller,* ibid., 1917, lxix, 765; and *Hektoen,* Jour. Infect. Dis., 1918, xxii, 28.

both of these types of protective substances may be formed during immunization, one or the other is usually preponderant.[1]

The antitoxic substances are most closely related to the globulins, but beyond this their chemical nature has not been definitely ascertained.[2]

The effect of antitoxin in the blood in rendering harmless the toxic substances which they form apparently is accomplished, not by the destruction of the toxins, but by a chemical union of toxin with antitoxin, whereby the former is deprived of its capacity to injure cells.

The knowledge of this antitoxic immunizing action of specially endowed blood-serum has been most fully developed in diphtheria and tetanus.

During the growth of the diphtheria bacillus in nutrient broth a toxic substance is developed which mingles with the broth. This is called diphtheria toxin, and subcutaneous injections of this toxin in animals—guinea-pigs, for example—prove fatal, in appropriate dosage, with symptoms and lesions similar to those caused by inoculation with the living germ. It has been found that by repeated injections of the diphtheria toxin in susceptible animals, at first with small, then with gradually increasing, doses, the animal may at length become so insusceptible to the action of the poison that many times the usually fatal dose is borne without sensible reaction. Similar immunity can be conferred in certain animals by the use of the living cultures of the diphtheria bacillus either fully virulent or with reduced virulence (page 194), administered at first in small doses which are gradually increased.

In whichever way immunity be conferred, it has been found that the blood of the artificially immunized animal contains a substance, or substances, called *diphtheria antitoxin*, which, on being introduced with the blood serum into other susceptible animals, may not only confer a quickly established immunity—passive immunity—but, without destroying the diphtheria germ, may protect against its toxic effects when the disease is already under way. Thus, through the artificial immunization of horses and the hypodermatic use of the serum of their blood in man, the so-called "serum therapy" has assumed a very important and beneficent rôle in the prevention and treatment of diphtheria.[3]

Results similar to those obtained in the study of diphtheria antitoxin have been realized in the investigations of tetanus. But the practical value of the tetanus antitoxin as a therapeutic agent is less obvious, as the toxin is rapidly fixed by the cells of the central nervous system and so

[1] The damage or destruction of bacteria by antibacterial, bactericidal, or bacteriolytic substances naturally limits or prevents the formation of toxic materials by the microorganisms, although the cells of the body may be very susceptible to the action of these. So that the absence of evidence of the establishment of antitoxic immunity in an infectious disease may mean, not that the body is incapable of this, but only that no opportunity is offered for its development.

[2] *Hiss, P. H.*, and *Atkinson, J. P.*, Jour. Exper. Med., 1900, v, 47.

[3] The antitoxic value or power of each specimen of antitoxic serum is experimentally determined by finding the amount of the serum required to protect the test animal against the action of a definite amount of toxin of known strength. Various standards have been adopted, the value of the serum being expressed in terms of the "antitoxin unit." For example, in the determination of antitoxin value made use of by the Department of Health of the City of New York, an antitoxin unit is the amount of antitoxic serum required to protect a guinea-pig weighing 250 grammes from death, when one hundred times the fatal dose of diphtheria toxin is mixed with the serum and the mixture injected subcutaneously into the animal. The usual dose for human administration may contain from three hundred to six thousand units.

becomes relatively inaccessible to the antitoxin. This does not detract from the value of the serum when exhibited early and in large amounts. Experience in the use of prophylactic injections of antitetanic serum in the past four years has shown its extraordinary value.

A serum against the toxins of the B. aërogenes capsulatus has recently been developed and seems to promise well. It has been shown, further, that antitoxic sera may be developed in the body during immunization to snake venom, the poison of the spider and scorpion, vegetable poisons, such as ricin and abrin, and to other albuminous animal and vegetable materials. Thus, also, through experimental adaptation, the living body-cells may elaborate and set free into the serum substances which suspend the action of ferments, like rennet, pancreatin, fibrin ferment, etc.

Not all toxic substances, however, are capable of inciting the living body to the formation of antitoxic substances; nor are these apparently formed in such considerable amount in most of the infectious diseases, as is the case in diphtheria and tetanus.

The action of these antitoxic substances is, within certain limits, specific; that is, the antitoxin of diphtheria protects against diphtheria, that of tetanus against tetanus, etc.[1]

EHRLICH'S "SIDE-CHAIN" HYPOTHESIS.

We have seen that a most remarkable series of facts is developed by our studies of infectious diseases illuminated by the results of animal experimentation. When the living body is invaded by a certain toxic complex organic material, not always of microbic origin, the body adapts itself to the new conditions by the elaboration of substances which protect it from the action of that poison. Each new protective substance is effective against the particular poison which induced its formation. Not only this, but if the blood serum containing these new protective substances be transferred to another individual they protect him also—passive immunity—against the special poison which called them forth in the body of the first.

How are we to conceive of this wonderful adaptive power of the living body under conditions which seem to be wholly new in the life of the individual; a power which at first appears to transcend the known capacities of the body-cells?

This singular capacity of the body-cells to develop in emergencies apparently new substances has naturally given rise to much study and to many speculations and hypotheses. The scope of this book does not permit even of enumeration of these. But it is necessary to bring forward at least in outline the so-called "side-chain" hypothesis of Ehrlich by which he strove to account for the phenomena of antitoxic immunity as exemplified with especial clearness in diphtheria and tetanus. Without his hypothesis we are to-day still practically at sea in our views of the nature of antitoxic immunity, while this remarkable capacity of the body to manufacture the greatest variety of potent specific antidotes to the most subtle and virulent poisons becomes, for the first time, comprehensible in the light of this ingenious conception. It is now several years since Ehrlich's hypothesis was enunciated, and, whatever may be its merit as a direct

[1] For a detailed consideration of the specificity of infectious agents, see *Kolle, W.*, Kolle and Wassermann, Handbuch. d. path. Mikroorganismen, 2d ed., 1912, i, 869.

The monograph by *Citron*, Die Methoden der Immunodiagnostik ûnd Immunotherapie (Eng. trans., 2d ed., Philadelphia, 1914) contains many facts of practical importance in the application of theories of immunity; while *Kraus* and *Levaditi's* Handbuch der Technik und Methodik der Immunitätsforschung (Jena, 1914) furnishes a most valuable survey of the entire subject from the point of view of method.

For a summary of the results of serum therapy, see *Kolmer*, Infection, Immunity, and Specific Therapy, 2d ed., Philadelphia, 1917.

contribution to science, there can be no doubt that it has been, in a remarkable degree, an inspiration to the most fruitful research. It is practically impossible to follow the recent work on immunity without a knowledge of this hypothesis and familiarity with the nomenclature to which it has given rise.

In order to comprehend the hypothesis of Ehrlich regarding the origin and nature of antitoxin, it is necessary for us to form with him a clear conception of cell assimilation.

We conceive of the cell as a mechanism for the storage of energy derived from without and for its release under definite conditions. This storage of energy is possible through the assimilation and building up by the cell of complex molecular combinations. These, owing to their instability, are readily changed into less complex and more stable combinations with the release of the stored-up energy. Thus is the life of the cell manifested.

This broad conception of the cell is a purely intellectual one, however, for the details of cell metabolism still elude the keenest scrutiny of the chemist. He cannot formulate protoplasm nor express its chemical changes by proportionate symbols.

Now, accepting this condition of affairs as for the moment inevitable, Ehrlich seeks to express his view of the character of the cell's performances in general terms, disregarding its morphological peculiarities, somewhat as follows: We may conceive of the cell as consisting of a central group of very complex molecular combinations which maintains the characteristics and special capacities of the cell as an organism under all

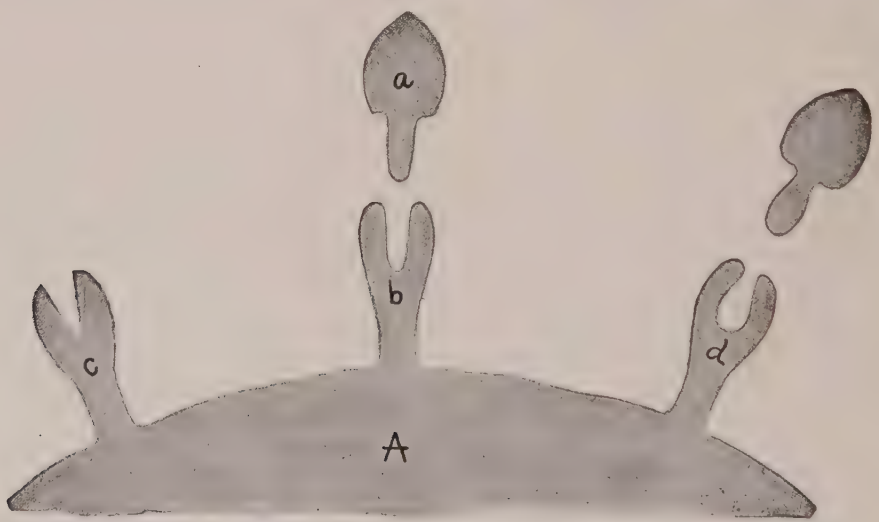


FIG. 114.—DIAGRAM ILLUSTRATING THE ACTION OF RECEPTORS IN THE NUTRITION OF THE CELL. *A*, Portion of cell body; *a*, food molecule; *b*, *c*, *d*, receptors.

the vicissitudes of its existence. Associated with this central organic group are many and various subsidiary atom-complexes which by means of their unsatisfied affinities bring the central group into relationship with food material through those chemical combinations which in living protoplasm characterize assimilation.

These unsatisfied affinities by which assimilable material is fixed or united to the cell have been called "side chains," a term adopted from the chemist. Not to press too closely, however, the analogy between the chemical processes in lifeless substances and assimilation in living matter, these affinities or "side-chains" of protoplasm are now commonly called *receptors*.

If we seek to illustrate Ehrlich's conception we shall be obliged to use graphic figures of extreme crudity. If the arc of a circle in Figure 114 represents a portion of

the periphery of a cell, we may indicate the side-chains or affinities or receptors by projections whose special shape shall indicate their special capacity to combine with any substance coming in contact with them under favorable conditions. Suppose in this figure we let *a* represent a nutrient molecule which is capable of combining with the receptor *b*, belonging to the cell *A*. Through its union with *b*, and only through this, is it capable of entering into the metabolism of the cell. This molecule *a* cannot unite with the receptor *c* or *d*, but only with such receptors—to use the crude expression which our illustration requires—as it fits. Through the receptors *c* and *d* other forms of food molecules may enter into the metabolism of the cell.

Thus it is in Ehrlich's conception, which after all is only a graphic way of illustrating the preliminary phases of assimilation by living protoplasm, that the cell is capable of selecting, or "fixing," out of the host of various substances with which it comes in contact, just those and only those to which its receptors bear a definite chemical relationship.

The same thing is true of toxic as of nutrient substances. In order to be toxic to the cell they must enter into chemical combination with a suitable receptor of the cell. Then only can they lead to the forms of damage which we are here considering.[1]

As the result of many studies on the nature and effects of toxins, Ehrlich was led to believe that the toxin molecule consists of two forms of affinities: one through which the chemical union with the cell is effected—called the haptophorous group; and the other—called the toxophorous group—by which the damage to the cell is brought about when once the toxin molecule is anchored to it.[2]

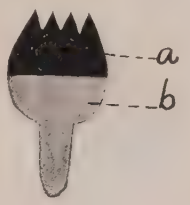


FIG. 115.—DIAGRAM ILLUSTRATING SUPPOSED CHARACTER OF THE TOXIN MOLECULE.
a, Toxophorous group; *b*, Haptophorous group.

This conception may be illustrated as in Figure 115, in which the toxophorous group *a* of the toxin molecule can be effective in damaging the cell only when united to the latter by the haptophorous group *b*.

Having now conceived of the living cell as consisting of a central essential complex molecular group, brought into relationship with its food materials by means of a great number of the most varied receptors, through which, under normal conditions, assimilation is secured, let us see what may happen if toxins come in contact with living cells which are furnished with receptors capable of uniting with them.

The union of the toxin molecule with the living cell being effected, the cell is more or less damaged. If the damage be sufficient, the cell dies. But suppose the damage to be but slight, as may be the case in artificial immunization or in early stages of an infection. The cell is at least deprived of the useful offices of the receptor to which the toxin molecule is now united. This is in itself a loss to the cell, and through the regenerative impulses common to all living cells it proceeds to regenerate the lost parts, which in this case are the receptors. But as more receptors are thrown out of function by the continued action of the toxin, the necessity for compensation continues.

Now it is a fact long known to pathologists, and especially emphasized by Weigert, that the regenerative impulse is apt to be in excess of the obvious requirements and leads to overproduction of new cells, tissues, chemical substances, etc. This is what now happens to the cells, some of whose receptors have been rendered useless by combination with the toxin. New receptors are formed, more than the cell requires; so

[1] It is evident, from what has been said about the conditions under which substances can be toxic, that the natural immunity of one animal to a given agent which is toxic in another may be simply due to the fact that the cells of the former have no receptors with which this agent can unite, or, if this union does take place, that the cell is not thereby damaged. This consideration has an important bearing upon our conception of natural immunity.

This so-called "fixing" or "binding" of toxin to tissues may be demonstrated by mixing some of the potent tetanus toxin with fresh brain tissue of the horse or guinea-pig, whereupon the mixture, if made in suitable proportions, becomes innocuous.

[2] Ehrlich was led to this belief in the complex nature of the toxin molecule through the curious fact that diphtheria toxin may under a variety of conditions lose its toxicity, but still retain its capacity of neutralizing antitoxin and also of uniting with cells, and thus inducing the formation of antitoxin in the animal body. Such toxin molecules deprived of the toxophorous group are called *toxoids*.

numerous may these become that many are at last cast off into the blood. Here is the point at last. *These receptors or substances, normal and useful to the body, but now formed in excess through over-compensation, and set free from the cells into the body fluids, are the antitoxin.*

For, set free in the body fluids, these superfluous receptors still retain their combining power for the free toxin molecules, which, also, are in solution in the body fluids, and unite with them. This union having been effected, the toxin molecules are no longer a menace to the cell, because the affinities are now satisfied through which they joined the receptors while these were still a part of the cell, and in this way could have become harmful. This now inert combination of toxin molecules and detached receptors is physiologically indifferent stuff, and may be removed from the body by the usual processes of excretion.

But the antitoxin which has not united with toxin in the body of the animal which produced it, is still available on the transference of the serum to another in-

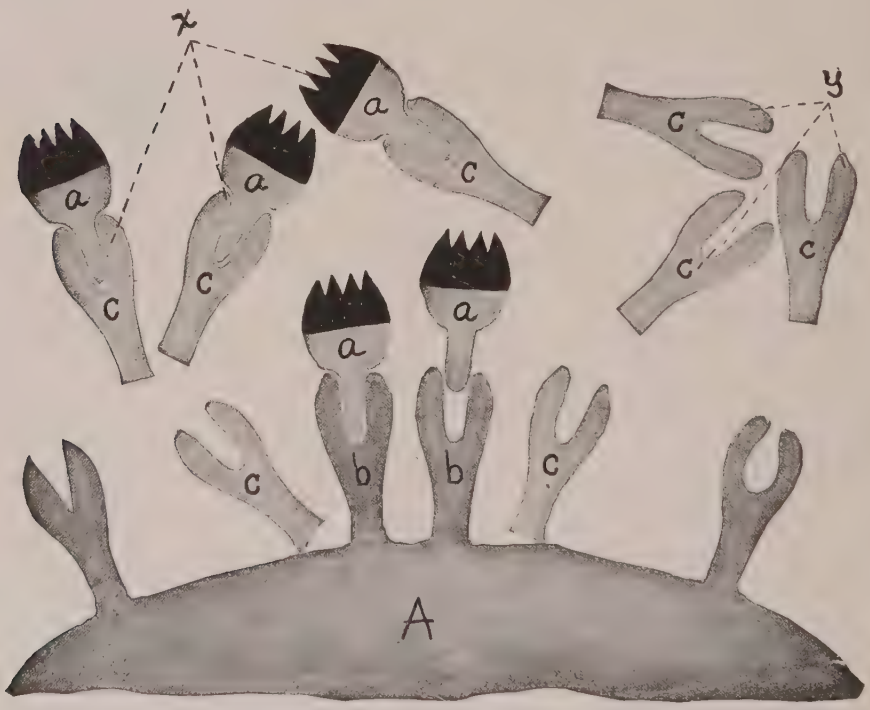


FIG. 116.—DIAGRAM ILLUSTRATING THE FORMATION AND ACTION OF ANTITOXIN IN ACCORDANCE WITH EHRLICH'S "SIDE-CHAIN" HYPOTHESIS.

A, Portion of cell-body; *b*, receptors combined with cell protoplasm; *c*, receptors separated from cell; *a*, toxin molecules; *y*, free receptors—antitoxin.

dividual whose blood contains diphtheria toxin, and who may thus secure passive immunity.

If we have recourse again to the graphic method, the hyperproduction of receptors by the damaged cell, their separation, and their action as antitoxin, may be indicated, as in Figure 116. Let *A* represent a portion of a cell-body. The toxic molecule *a*, uniting with the receptors *b*, leads through the injury to the cell, as well as by its deprivation of the normal use of *b*, to the production, and at length to the overproduction, of new receptors of the same kind. These superfluous receptors *c* are now set free

into the body fluids,[1] where, as at x, they may freely unite with the toxin molecules, forming harmless compounds and preventing further access of the toxin to the cell, where alone the damage can be done. Or, when free, as at y, the receptors may be transferred in the serum, becoming effective as antitoxin in another individual.

It is well to note that so long as the receptor maintains its connection with the cell it is not antitoxin, but an element of vulnerability to the cell. It is only when the receptor has been set free from the cell that it is antitoxin.

The antitoxin substance which neutralizes the action of the toxin molecule of diphtheria is not effective for the poison of tetanus, for example, simply because it does not combine with the molecule of tetanus toxin. It *is* specific for diphtheria, because it was the diphtheria toxin which excited its overproduction through a chemical union identical in character, whether this union takes place while the receptor is a part of the cell, in which case the toxin becomes harmful, or when the receptor is detached from the cell, in which case the combination is harmless.

In the light of this hypothesis the specific character of the antitoxic substances appears to be but the result of adaptation to unusual conditions of cell capacities evolved and fostered for the every-day maintenance of life. The specific relationship between the toxin and the antitoxin is not developed during immunization, but existed beforehand as a necessary condition of toxic action.

This hypothesis not only accounts for the formation, protective action, and specificity of antitoxin, but reveals, also, a special significance in the incubation period, during which the conservative forces are mustering. We can realize, furthermore, in the light of this hypothesis, how it is that the protection secured in active immunization is less immediate and also why it is more prolonged than in the passive, since in the latter the available antitoxin is limited to the dosage and is not replenished as in active immunity by the continued cell activities of the affected individual himself.

The conception of Ehrlich as to the nature of antitoxin is that of the chemist, and carries over to the performances of protoplasm the presumptions upon which chemical reactions in general are conceived and formulated. But this is not an easy matter, since our knowledge of the ultimate phases of protoplasmic metabolism is very incomplete. The physiological chemist presents to us as his final achievement in analysis an extremely elaborate complex which he calls the protein molecule. This he does not yet venture to formulate. Thus it is that when we attempt to illustrate in graphic fashion our conception of the performances of protein molecules, either in normal metabolism or in poisoning, we are forced to use the crudest of symbols. The use of such symbols is not without hazard, for these toxins and these receptors are, in truth, not histological structures, but molecular groups; they are not alone upon the surfaces, but through all the mass, of the protoplasm. They do not "break" off from the cell, but are set free as are other chemical substances which result from molecular transformations. Thus, if one cannot at last translate these uncouth symbols into the nice conceptions of the chemist, they will prove but stumbling-blocks.

There has been much discussion of Ehrlich's hypothesis, and it has withstood many assaults, mostly inspired by misconceptions of the fundamental claims. The scope of this book does not permit us to consider the many and ingenious experiments by which this view of antitoxic immunity has been sustained, nor is it practicable now to call attention to many of the phenomena not yet accounted for or seemingly inconsistent with the interpretations here set forth.

It is a working hypothesis which no doubt indicates but crudely the nature of the subtle processes concerned, as must indeed be the case while our knowledge of the phases of energy which sway and determine life is still very meager; but it has already inspired much fruitful research which is an important feature of working hypotheses in whatever field, and whatever their ultimate fate.[2]

[1] These receptors of various kinds, cast off into the body fluids under the most diverse conditions Ehrlich called "haptines."

[2] For a general criticism of Ehrlich's hypothesis from a physicochemical aspect, see *Arrhenius*, Immunochemistry, New York, 1907.

Bactericidal or Antibacterial Immunity (Bacteriolytic Immunity.)

General Considerations.—An extended series of studies on artificial immunization has shown, as we have seen, that the protection is secured by the formation of antitoxic substances in relatively few instances, notably in diphtheria and tetanus, whose inciting bacteria set free in cultures, as in the body, soluble toxins of great potency. Nevertheless, when in some of the ways detailed above (page 193) an animal has been gradually adapted to cultures of pathogenic bacteria either living or dead, or to their products, it has been found that the body fluids do contain protective substances. The protective action in these instances has occasionally been shown to be associated with the induction of morphological changes in bacteria which indicate their damage or destruction—bacteriolysis. Active immunization in man with the dead bodies of their respective bacteria has been widely practised in typhoid fever, Asiatic cholera, and plague, with apparently favorable results, while the use of the serum of immunized animals, in these and certain other diseases, has not been thus far very encouraging in conferring passive immunity.

While, therefore, the data at hand in those artificial immunizations which are not antitoxic, point to the bactericidal and bacteriolytic action of substances developed in the body as the important, if not the dominant protective factors, there may be many other processes contributing to the same end, which are as yet not clearly defined. Thus, there may be increased phagocytosis; vulnerable body-cells may become less susceptible, the growth of bacteria may be inhibited though they be not destroyed, etc. But these possibilities cannot be discussed here.

Furthermore, it should not be forgotten that the antitoxic action of protective sera may often be associated with those agents which directly damage the infecting organism.

As regards the destruction of bacteria in the body, we have seen that this may take place directly through the action of phagocytes or by the action of the body fluids. But the details and exact nature of this destructive process have been extremely difficult of study, owing to their complexity and the minuteness of the microorganisms. Of late, however, a series of remarkable studies in a related field have led to a clearer conception of the ways in which bacteria and many other alien organic substances are destroyed in the body, under ordinary circumstances as well as under the special conditions which infection involves.

"Pfeiffer Phenomenon."—Some time ago, Pfeiffer[1] showed that the blood serum of a guinea-pig artificially immunized against the cholera vibrio, was capable, under certain conditions, not only of immobilizing and killing cholera germs in a short time, but also of causing their disintegration and destruction. This significant capacity of immune serum was, after a long series of experiments, finally found to be due to two distinct substances. One of these appeared to be formed in the body, as the result of the gradual adaptation of the animal to the cholera

[1] *Pfeiffer*, Ztschr. f. Hyg., 1894, xvii, 355.

microbe, and was called the *immune substance.* The other seemed to be normally present in the serum of the warm-blooded animals, and to be identical with the substance which had long been regarded as in itself germicidal, and which had been called by Buchner *alexin.* It was presently found that lysis of the cholera microbe occurred only when these two substances act together, neither of them when separate having lytic power. If the two substances, the immune substance and the alexin, lytic when together, are heated to 56° C., the lytic capacity is lost. But if a small amount of fresh blood-serum containing alexin be now added, the lytic power is at once restored. These curious facts, set forth in part by Pfeiffer and further developed by Bordet and Metchnikoff, obviously have a significant bearing upon our conception of the processes by which those phases of immunity are secured in which the destruction of microorganisms plays an important part.

But the study of the effects of lytic sera upon bacteria is one of great technical difficulty, so that it is only since an important series of observations were made upon the lytic action of the body fluids on other and more easily studied forms of cells that our conception of the nature of bacteriolysis has become at all clear.

It is therefore necessary for us to look briefly at a new line of research bearing upon bacteriolytic immunity which has already led to most significant results and opened biological fields of great scope and complexity.

CYTOLYTIC SUBSTANCES—CYTOLYSIS.

Hemolysins—Hemotoxins.—It has been known for nearly fifty years that the blood serum of one animal species, when injected into the vessels of another, may do serious damage and even kill the latter through a rapid separation of the hemoglobin from the red blood-corpuscles. This dangerous effect brought to a speedy end attempts which were at one time made to sustain the ebbing forces of life by the transfusion of alien blood. But the significance of this so-called "laking" of the blood by mixture with alien sera was overlooked.

Bordet, however, in 1898, inquired whether, if the animal body be capable of adapting itself to toxic substances and to bacteria in such a way as to neutralize the effects of toxins and to destroy bacteria as had been shown by earlier experiments, it may not respond similarly to the introduction of other foreign substances such as alien red blood-cells, for example.

The blood serum of the guinea-pig is not normally lytic for the red blood-cells of the rabbit; that is, it does not cause the separation of the hemoglobin from the stromata, with a partial destruction of the latter.[1] Now, Bordet injected a few cubic centimeters of the defibrinated blood of the rabbit, containing the serum and red blood-cells, into the subcutaneous tissue or peritoneal cavity of normal guinea-pigs. This operation, which does not markedly interfere with the well-being of guinea-pigs,

[1] While the serum of the guinea-pig is not normally lytic for the corpuscles of the rabbit, the serum of the rabbit is lytic for the corpuscles of the guinea-pig. Similarly, normal rabbit serum is not lytic for the beef corpuscles, but beef serum is lytic for the corpuscles of rabbits and guinea-pigs.

was repeated five or six times at intervals of a few days. When blood was drawn from the treated pig, allowed to clot, and the clear serum secured, it was found to have become markedly lytic for rabbit corpuscles. A very small proportion, mixed with rabbit's blood diluted with physiological salt solution, in a short time brought the hemoglobin into a clear ruby solution in which the stromata or "ghosts" of the corpuscles floated as a pale and scarcely visible cloud. This process is called *hemolysis;* serum possessing this capacity is called *hemolytic* or *hemotoxic* serum.

This adaptation of one animal to the red blood-cells of another species may be accomplished without difficulty with a great variety of animals.

But a most remarkable thing about this newly acquired lytic capacity of the serum is that it is limited to the red corpuscles of the species of animal whose blood was used for the injection—in Bordet's experiment to the corpuscles of the rabbit. Red blood-cells of the dog, cat, sheep, ox, fowl, etc., are no more affected by this serum of a guinea-pig which has been adapted to the blood of the rabbit than they were before. In other words, the adaptation to foreign corpuscles is specific.

The statement that this adaptation to alien blood is specific—that is to say, that the serum becomes active only for the corpuscles of the species injected—should be so qualified as to recognize the curious fact that a slight degree of lysis may often be induced in corpuscles of species of animals very closely related to those from which the injected blood is derived. For example, if a rabbit be adapted to human blood by intraperitoneal injections, the serum of this rabbit, now strongly lytic for the corpuscles of man, may be slightly lytic for the corpuscles of monkeys. Similarly, serum artificially lytic for the red cells of goats may be slightly lytic for those of sheep, but not for the corpuscles of cats, dogs, man, etc. (See, for technique of hemolysis tests, page 228.)

This form of test, delicate beyond anything hitherto known in physiological chemistry, may thus prove of value in defining the relationships and limitations of animal species.[1]

This preliminary observation of Bordet was followed by a series of studies upon artificial hemolysis, the results of which we can only briefly summarize. In the first place, to what is this remarkable acquired lytic capacity of the serum due? Bordet heated for half an hour at 56° C. some of the lytic serum secured by adapting the guinea-pig through subcutaneous injections to the red blood-cells of the rabbit. He found that it had completely lost its new lytic power. Such serum is said to be *inactivated.* But when he now added to this inert serum a little fresh blood-serum from a normal guinea-pig, which is not in itself lytic (page 203), the original dissolving power of the heated serum for rabbit corpuscles was at once restored—*reactivated.* The inference from this experiment is obvious. The dissolving capacity of this artificially lytic serum is due to two distinct substances. One of these, that one which results from the adaptation of the animal to the alien blood, is stable

[1] For further data on this subject, see *Nuttall,* Blood Immunity and Blood Relationship, Cambridge, 1904.

at 56° C.; the other, which is present in normal serum, is rendered inert at 56° C.; that is, it is very labile. These two substances were named early and have been often renamed. For the present we may speak of the stable substance resulting from the adaptation to the alien blood as the *immune substance* or *immune body*, and of the other, more sensitive to heat, present in normal serum, and not increased in the processes of immunization, as *alexin*, a name which was long ago applied by Buchner to a substance or substances in normal serum, to which its germicidal capacity, first clearly demonstrated by Nuttall, was attributed. This alexin is now called *complement* for reasons given on page 210.[1]

There now followed a series of important studies by Ehrlich and his associates which throw still further light upon these curious lytic agents.

Separation of Alexin and Immune Substance.—We have seen that in order to secure the immune substance free from the alexin one has only to heat the lytic serum to 56° C. for half an hour, when the alexin is destroyed. If one wishes to secure the alexin apart from the immune substance he makes use of a very curious property of the latter; namely, its capacity of uniting with the cellular element under whose influence it was elaborated. For example, if one places a small portion of the serum of a rabbit which has been adapted to beef blood in contact with beef corpuscles at a low temperature[2] for a few hours, he will find that the immune substance has formed so stable a combination with the corpuscles that on their separation from the fluid by centrifugation in the cold, none of the immune substance, but all of the alexin, will be left in the fluid.

That the corpuscles under these conditions actually contain the immune substance is readily shown by carefully washing them in salt solution and centrifuging them again in the cold and finally adding to them a little normal serum—containing alexin, but no immune substance—whereupon the lysis will at once take place, as shown by the red color of the fluid. This union of the immune substance with corpuscles, called "fixation" of the immune substance, is specific, occurring only with the corpuscles of the animal species used in the adaptation. The alexin may also be absorbed by a number of substances, including emulsified tissues, tissue extracts, yeast cells, bacteria, and even inert substances such as kaolin. Of its chemical nature nothing is known. It was at one time supposed to be of lipoid character, but this view has not been sustained.

Many other points of extreme interest and significance have been revealed in these studies on artificial hemolysis which the scope of this book does not permit us to touch upon.

Multiplicity of Immune Substances and Alexins.—The question of a multiplicity of immune substances and of alexins has been brought forward, and it seems probable, especially from the researches of Ehrlich,

[1] It has been found that the hemolytic capacity of the *normal* blood serum, which in many animals as we have seen, is very marked for the corpuscles of alien blood, is also due to two substances which in character and action are similar to those which have been so carefully studied in the lytic sera of artificially adapted animals.

[2] It is necessary to reduce the temperature in this experiment in order to inhibit the action of the lytic agencies.

that in adaptation of each animal species to a single form of cell several immune bodies may be developed. It is possible, though not yet proved, that more than one alexin may be normally present in the blood serum of each animal species, and that a single immune body may be capable of uniting with several forms of alexin.[1]

Bacteriolysis.—It is evident that this artificial hemolysis, secured by the adaptation of one species of animal to the red blood-cells of another, is quite analogous to the process by which immunity is secured against pathogenic bacteria—those of cholera, for example, whose most obvious poisonous elements are endotoxins—and which is called *bacteriolysis*. Both are specific examples of the general process called *cytolysis*, meaning cell destruction. This reaction of hemolysis is one of extraordinary delicacy, and is easily observed under conditions quite within our control; and it is useful as an aid to the understanding of such elaborations and variations as involve great technical difficulties when we are directly engaged with the phenomena of bacteriolysis.

Thus these studies of hemolysis have a practical significance in their bearing upon our conceptions of bacteriolytic immunity quite apart from the interesting general biological field into which they have led the way.[2]

Special Cytolysins—Cytotoxins.—The development of cytolytic capacities in the blood-serum of the living animal as the result of adaptation to bacteria and to alien red blood-cells being known, it was natural to extend the method to other cells. Thus it has been asserted that in the adaptation of one animal to the spermatozoa of another species by intraperitoneal injections, a serum is obtained which quickly brings to an end the movements of fresh spermatozoa of the species used—*spermolytic* serum.

There have been produced many other cytotoxic sera which were thought to have specific action on the cells of the organs used as antigens, and it was expected that much light might be thrown upon the nature of many of the degenerative lesions which occur in the organs, especially the liver and the kidney, and that an approach might be made toward a specific therapy of cancer; but such is not the case. While a nephrolytic serum when injected may give rise to extensive lesions of the kidney, similar lesions are produced in other organs, also; and the effects seem due mainly to the hemagglutinative power of such sera, causing capillary thrombosis.[3]

It appears, therefore, that cytotoxic specificity is not so much a matter of cell morphology as of molecular structure, and that an organ-specific serum is not obtainable. In this connection it is of interest to recall that five separate antigens have been demonstrated in protein of the hen's egg.[4] Autocytotoxins cannot in general be produced.

[1] See, for general review of the alexin question, *Zinsser*, Infection and Resistance, 2d ed., New York, 1918.

[2] For technic of hemolysis experiments and the adaptation of animals to alien substances see pp. 228 and 230.

[3] *Pearce, R. M.*, Jour. Exper. Med., 1906, viii, 64.

[4] *Wells, H. G.*, Jour. Infect. Dis., 1913, xii, 341. For an interesting study of the chemical individualities of tissue elements and their biological significance, see *Levene, P. A.*, Jour. Am. Chem. Soc., 1917, xxxix, 828. See, for in vitro tests showing non-specificity of cytotoxins, *Lambert, R. A.*, Jour. Exper. Med., 1914, xix, 277.

So far as they have been studied, the nature of the active agents in these various cytolytic sera and their mode of action are analogous with those in hemolytic sera. Here, as there, the action is due to two groups of substances: one, the "immune body," stable and increased by the adaptive process; the other, the alexin, occurring normally in the body, not increased in adaptation, and readily destroyed or rendered inactive by heat.

All of these last-mentioned forms of cytolytic sera require more extended study before far-reaching conclusions should be drawn from them. But it is now evident that the different functional types of cells in one animal are capable, in the adaptation to the economy of another, of inciting more or less definitely specific responses, as shown by the various types of cytolytic sera which are formed.

When one musters all the possible combinations in this form of adaptation and considers the probability that multiple immune bodies may develop in each instance, and that these, furthermore, may correspond to multiple alexins, the complexity of artificial cytolysis becomes evident.

Antigens.—We have seen that the introduction into the living organism of alien protein substances of many kinds, derived from animals or plants, some of them poisonous, many of them not, incites the formation of so-called antibodies of divers sorts. It has been found convenient to call these "antibody producers," or "antibody incitors," *antigens.*[1] They are probably all protein in nature. It has not been shown that fats, lipoids, or carbohydrates can act as antigen.[2]

Anticytolysins.—But now still another phase of this subject demands a word. These cytolytic or, as some prefer to call them, cytotoxic sera, when introduced into the living bodies of the species from which the cells inciting their formation are derived, act as toxins to which the organism responds, each after its kind, by the development of antitoxic substances. These are called *anticytolysins* or *anticytotoxins.*

Let us look at an illustration of this interesting point. The blood serum of the normal guinea-pig has, as we have seen, no lytic action on the red blood-cells of the rabbit, but after the adaptation of the guinea-pig to the blood of the rabbit by repeated intraperitoneal injections, the guinea-pig serum is strongly lytic for the rabbit corpuscles in test-tubes outside the body. But this lytic serum is not less toxic when introduced into the body of the rabbit. Under these conditions the rabbit, if it survives, produces an antitoxin, an antihemolytic substance, which is in solution in his serum. If a little of this antihemolytic serum be mixed with some of the lytic serum from the adapted guinea-pig, it will be found, on the addition of rabbit corpuscles, that the lytic serum has lost its power, just as diphtheria toxin loses its harmful properties on mixture with diphtheria antitoxin. Thus may be formed a great variety of specific "antibodies"—anticytolysins—from sera which are normally lytic or have become so through experimental adaptations.

[1] For a study of the locus of antibody formation see, *Hektoen* and *Curtis*, Jour. Infect. Dis., 1915, xvii, 409; *Hektoen, L.*, ibid., 1915, xvii, 415; 1918, xxii, 28; *Simonds* and *Jones*, Jour. Med. Research, 1915, N. S. xxviii, 183; ibid., p. 197; *Becht* and *Leuckhart*, Am. Jour. Physiol., 1916, xl, 366.

[2] *Kolmer*, Infection, Immunity, and Specific Therapy, 2d ed., Philadelphia, 1917, p. 161.

Isolysins and Autolysins.—In view of the remarkable results of the adaptation of the body to alien cells from different animal species which we have reviewed, it was natural to ask how an animal would respond to the introduction into the recesses of his body of cells—red blood-corpuscles, for example—from another individual of the same species. It was found, in fact, that under these circumstances lytic substances are sometimes, though not uniformly, developed. The possibility of the formation of *isolytic* substances was thus established. But if this be possible, why, it was asked, may not *autolytic* substances be formed by the adaptation of an animal to his own cells experimentally displaced? Such substances have, however, not been found under the experimental conditions thus far observed. The spontaneous occurrence of isolysins and isoagglutinins in human blood is, of course, well known (see chapter on Blood).

It has been demonstrated (see page 118) that cells and tissues worn out from use, or dead as the result of injury, inflammatory exudates, etc., are constantly removed from the living body by processes apparently analogous to, if not identical with, those which can be experimentally evoked; so that autolysis in some form seems to be an important factor in the maintenance of the integrity of the body (see page 126). Just what the agencies are under which normal living tissue cells are protected from the action of autocytolytic substances is not yet clear. But the multiplicity of known "antibodies" justifies the conjecture that such substances—anticytolytic—may be constantly formed and act as safeguards to living and useful cells (see page 199). Many of the phenomena of autolysis, however, are unquestionably due to the release, on the death of the cell, of ferment activities contained in its own cytoplasm. These proteases seem to be present in all body-cells except perhaps the red corpuscles.

The Application of Ehrlich's Hypothesis to Cytolysis.—If we now turn to the various hypotheses which have been advanced to account for the formation and action of these cytolytic substances, we find that an elaboration of Ehrlich's views as applied to antitoxin is here a source of great illumination. It is evident at once, however, that the matter is not so simple as in the case of antitoxin, because we have here two substances at work, the immune body and the alexin. Neither the immune body nor the alexin alone induces cytolysis. They must act together.

The phenomena are, in the main, accounted for if we assume that it is the alexin which, when the necessary conditions are fulfilled, exerts the destructive action upon the bacterial or animal cell. But the alexin cannot enter under ordinary conditions into direct chemical combination with the cell receptors. The union is effected only by the intervention of the substance which is increased in amount in the process of adaptation; namely, the immune body.

A long series of experiments has led to the belief that the immune body has two free atom complexes which enable it to form chemical unions. Through one of these atom complexes it unites with the cell or bacterium to be destroyed; through the other it is joined to the alexin. Then, and not until then, is the alexin so linked to the cell that its toxic or destructive action upon the cell occurs.

This conception may be illustrated, as in the case of antitoxin, by crude figures.

Here it should be remembered we are illustrating, not the production of the cytolytic substances, which we shall speak of later, but the action of them upon the cells to be destroyed.

Let *a*—Fig. 117, A—be the cell which is to be destroyed, with one of its receptors indicated at *d*. Let *b* represent the immune body with one atom complex *e* capable of uniting with the cell receptor *d*, and with another *f* capable of uniting with the alexin *c* through *g*. Now the alexin which appears to be the effective agent in the destruction cannot unite directly with the cell receptor. When, however, it becomes linked to the cell by means of the immune body, *b*, its destructive capacity can come into play.

In a similar way one may indicate the action of anticytolytic substances which may be effective through union either with the alexin or with the immune body, as shown in Figure 117, *B* and *C*. In *B* the "antibody" *h* prevents the linking of the alexin *c* to the immune body *b* by itself uniting with the former. It then acts as an antialexin. In *C* the antibody "*i*" prevents the linking of the immune body *b* to the cell receptor *d*, and hence acts as an antiimmune body. We shall see in a moment why at present the substance here spoken of as antialexin is usually called the anticomplement.

The experimental evidence that the anticytolytic substances may be thus due to the formation of adaptive substances of two classes, antiimmune substances and anticomplements, cannot be entered upon here.

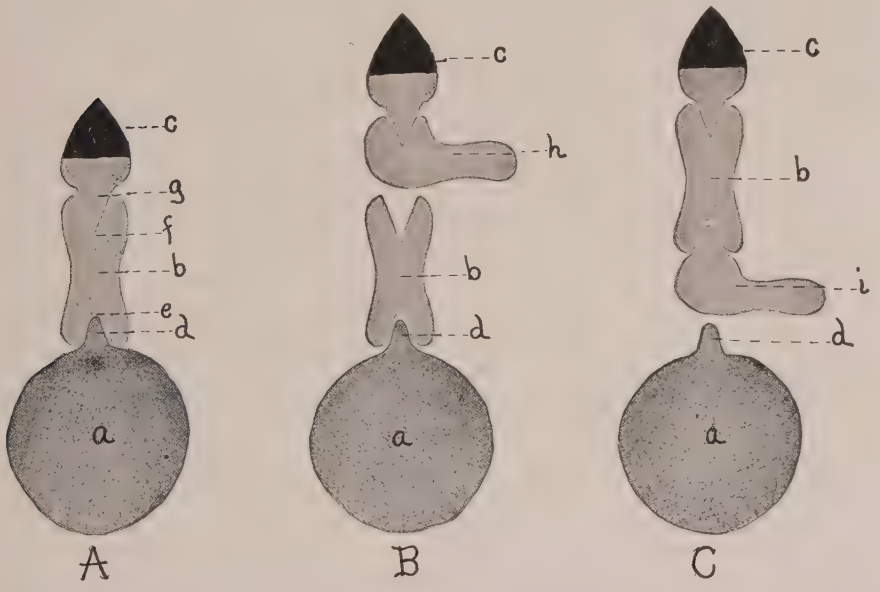


FIG. 117.—DIAGRAM ILLUSTRATING CYTOLYSIS IN ACCORDANCE WITH EHRLICH'S HYPOTHESIS.

A—*a*, Cell; *b*, immune substance (amboceptor); *c*, alexin (complement); *d*, cell receptor; *e*, atom complex of the amboceptor capable of uniting with the receptor, *d*; *f*, atom complex of the amboceptor capable of uniting with the haptophorous group, *g*, of the complement, *c*.

B—*a*, Cell; *b*, immune substance (amboceptor); *c*, alexin (complement); *d*, cell receptor; *h*, antialexin (anticomplement).

C—*a*, Cell; *b*, immune substance (amboceptor); *c*, alexin (complement); *d*, cell receptor; *i*, antimmune substance (antiamboceptor).

In view of the rationale of cytolysis, as just set forth, we may consider the immune substance to be an intermediary between the alexin and the cell to be destroyed; or, on the other hand, we may consider the alexin as the complement to the immune substance, since only through their union is the toxic action possible.

In fact, following Ehrlich, one sometimes speaks of the immune body as the *intermediary body*, or *intermediary substance;* but since it is furnished with two combining affinities, it is now usually called the *amboceptor*. Furthermore, since the experimental analysis of the lytic process by the new technique has shown that the germicidal and destructive action of blood-serum, formerly supposed to be due to a single substance

called alexin, is really due to the combined action of two substances, the use of the word alexin for one of them is misleading and has now been largely given up. The substance present in the serum of both normal and adapted animals through which lysis is effected when it is linked to the cell by the amboceptor is called the *complement*. Other names have been applied to these hypothetical complexes or substances which we cannot consider here.[1]

This, then, is the rationale in accordance with Ehrlich's hypothesis of the action of these cytolytic or cytotoxic substances, either existing naturally, as they do in some animals, or being called forth in larger quantities in the process of adaptation to the cells which they destroy. This view has been most fully tested upon hemolytic sera, since here the reaction is most easily studied. But so far as one can see, it applies as well to the phenomena of bacteriolysis, whose direct study is much more difficult. It should, however, be borne in mind that the erythrocytes are very delicate and very peculiarly constituted cells, and it is possible that inferences drawn from hemolysis are not applicable without qualification to other and less vulnerable cell types.

The origin of the amboceptors of these cytotoxic substances is accounted for in the same way as in the case of antitoxin. The alien cells or substances which are introduced into the animal, and to which it proceeds to adapt itself, lead, through union with such body-cell receptors as may be fitted to them, to the overproduction of these special complex receptors. These are presently cast off as superfluous to the body-cell producing them, and are then free as amboceptors in the body fluids.

As in the case of antitoxin formation, it is probable that the cell receptors which are thus increased are normally concerned in cell assimilation, and it is not unlikely that their complex character may have some relationship with the complexities of the "giant" protein molecules, which must suffer initial changes before becoming fit for assimilation. At any rate this hypothesis assumes that in the process of adaptation either to toxic substances or to foreign cells or other protein material, the body develops no new capacities, but only an exaggeration of those already existing.

As to the exact source of the amboceptors in artificially immunized animals we cannot yet speak with certainty, but the experiments of Hektoen[2] point strongly to the fact that they are produced in the lymphatic tissues, the spleen, and the bone-marrow; for if animals are exposed to large doses of x-rays, they do not develop antibodies. It is not possible, however, to exclude the occurrence of serious injury to other organs, though morphologically the chief damage seems to be to the hematopoietic system.

The Action of Phagocytes in Cytolysis.—It was inevitable that the remarkable studies on cytolytic sera just summarized should have led to a clearer conception of the manner in which phagocytes destroy bacteria and other organic substances. It is no longer permissible to hold as distinct and unrelated processes the action of phagocytes and the action of the body fluids in the destruction of foreign substances in the body.

Metchnikoff, the learned and able advocate of the importance of phagocytosis in the protection of the body against microorganisms,

[1] It was natural in the early studies on bacteriolysis, which were incidental to researches on immunity, that the new substance which was found in the serum as the result of the immunizing process should be called the immune substance or immune body. It was natural also, although less appropriate, to apply the same term, "immune substances," to the analogous substances which appeared in the serum as the result of the injection in the same fashion of cells and other materials which were not infectious, not disease-producing, and against which, therefore, the body is not, in the old sense, immunized.

But these new uses of the word are, I think, unfortunate because the word "immunity" has come to have a special and useful significance in relation to infection, intoxication, and other conditions of natural or acquired tolerance to obviously and seriously harmful agents. The process in both instances is, indeed, one of adaptation, and the newly acquired capacities of the serum are due to substances resulting from this adaptation. They arise from a functional modification of parts of the body, and hence may be appropriately called adaptive substances. It seems to the writer that it would be better to consider immunization as a special phase of adaptation, and so limit the application of the word that it shall still connote infection and intoxication in the traditional sense.

[2] *Hektoen, L.*, Jour. Infect. Dis., 1918, xxii, 28.

recognized the importance of the adaptive substances, some of which may be largely increased in amount in the processes of immunization. More strenuously than other observers, however, he insisted upon the phagocytic cells, especially the leucocytes, as the originators of the substances concerned in cytolysis, and held that under ordinary conditions it is only within these cells that these substances are effective. In artificially immunized animals, however, the intermediary substances, it was conceded by Metchnikoff, may be set free from the cells which produce them and mingle with the body fluids. The complement, on the other hand, which he, in common with others of the French school, called *cytase*, in recognition of its ferment-like characters, Metchnikoff did not believe to be set free in the body fluids except through some damage to the leucocytes in which it is formed; such a damage, for example, as befalls the leucocytes in the clotting of the blood; for in this process it is assumed that the setting free of the fibrin ferment involves the destruction—phagolysis—leucolysis—of the leucocytes.

The views advanced by Bordet and others of the French school regarding the union of the amboceptors with the cells to be destroyed are less precise than those of Ehrlich. Both, however, recognize the importance of an association of the amboceptor as a condition for the effective action of the complement (*cytase*). It is for this reason that the amboceptor is called by Bordet, Metchnikoff, and others, the sensibilizing substance (*substance sensibilisatrice*) or the fixative (*fixateur*).

Finally, a long and ingenious series of experiments has led Metchnikoff and his associates to believe that there are two forms of *cytase*, one called *macrocytase*, formed by the macrocytes (large lymphocytes derived from the spleen, lymph-nodes, and certain endothelial and connective-tissue cells) and concerned in the destruction of animal cells, such as red blood-cells, leucocytes, spermatozoa, various parenchyma cells, etc.; and *microcytase*, derived from the microcytes (polymorphonuclear leucocytes), which is active in the destruction of bacteria (see page 124).

The greatest diversity of view concerning the cytolytic process between Metchnikoff and his followers and the observers of the Ehrlich school relates to the question whether the complement (*cytase*) does or does not exist free in the blood plasma, for upon the answer to this question depends largely our belief as to the relative significance of intra- and extracellular cytolysis. This is one of the points concerning which more data are urgently needed. But even now the views of Metchnikoff are not inconsistent with the hypothesis of Ehrlich, and the present tendency is to revert to the opinions of the French school as simpler and equally logical in the explanation of the phenomena.

There is reason to believe that bacteria are destroyed within phagocytes by the action of enzymes[1] in a manner analogous, at least, with that of their destruction in the bacteriolytic fluids which we have just considered. But just how these intracellular processes are fostered by protective sera is not clear.

[1] See *Opie, E. L.*, Jour. Exper. Med., 1906, viii, 410, 536.

AGGLUTINATIVE SUBSTANCES.

Agglutinins.—There are important adaptive resources of the living body, when it is called upon to deal with foreign material of special character introduced in unusual ways into its recesses, in addition to those just considered.

The phenomenon of agglutination has been widely known for several years, especially on account of its practical application in diagnosis. The general fact is that as an individual adapts himself—that is, becomes immunized—to a special bacterium or its toxic products, either in the course of an infectious disease or as the result of artificial processes, his serum, if placed under suitable conditions in contact with cultures of this special microorganism, may speedily immobilize the organism if it be motile, and, whether motile or not, lead to its clumping into irregular masses. This reaction has been used, not only as a clinical test of special infections,[1] but also as a means of differentiating species or varieties of bacteria.

GROUP AGGLUTINATION.—But the serum of an animal adapted to a particular bacterial species sometimes has the power of agglutinating closely related organisms, such, for example, as the interagglutinations of the colon-typhoid group.

However, the organism used for adaptation—the so-called "homologous" organism—usually agglutinates in so much greater dilutions than do the other organisms of this group—the heterologous organisms—that with due care, in spite of the group agglutination, the test is useful.

Recent studies have emphasized the fact that agglutination is a much more general phenomenon than has been commonly supposed, and is by no means limited to the sera of animals immunized against bacteria and bacterial products, for hemagglutinins for human corpuscles are present in the blood of certain normal persons; even autoagglutination has been found to occur.[2]

The interesting problems involved in the application of our knowledge of isoagglutinins and isohemolysins to transfusion will be found discussed in the chapter on the blood (page 535).

For example, in the adaptation of one animal to the red blood-cells of another species, the serum of the adapted animal may become not only lytic but agglutinative also for the corpuscles used for the injections. This is true not only in adaptation to red blood-corpuscles but to other cells as well. We have, then, to add agglutinative substances or agglutinins to the list of those which are developed in the body in this form of adaptation. These also, within the limits already set forth, are specific.

Just as the specific red blood-cells are capable of "fixing" the immune substance in lytic serum, so also the agglutinating substance may be "fixed" and removed from serum by placing in contact with the serum

[1] For the general demonstrative tests for agglutinin, see p. 228. For details of special applications of the agglutination test, see *Wood*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917, or other works on clinical pathology.

[2] For a study of a case of autoagglutination in man, see *Clough* and *Richter*, Bull. Johns Hopkins Hosp., 1918, xxix, 86.

some of the corpuscles of the particular animal species or some of the bacteria under whose influence the agglutinative substances were formed.

While agglutinative substances are developed in the process of immunization, they are not, so far as we know, directly protective, though by the grouping of microorganisms the action of phagocytes may be favored. The virulence of pathogenic bacteria is not reduced by agglutination.

The agglutinative seem to differ in many ways from the lytic substances. Thus their activities are not suspended by a temperature of 56° C. They become inert, however, at a higher temperature—70° to 78° C.—and their agglutinating capacity is not restored by the addition of normal serum; in other words, their activities are independent of complement and, in all probability, are largely of a physicochemical nature. It is inferred from this fact that the receptors concerned in agglutination are of simpler character than those through which lysis is secured.

The normal blood-serum of some animals contains substances which are agglutinative for the red cells of other species. Thus, normal beef serum is agglutinative for the corpuscles of the cat and rabbit. This capacity of the normal serum sometimes is, sometimes is not, associated with marked lytic capacity. Isoagglutinins, either with or without isohemolysins, are frequent in human blood.

The mode of action of these various agglutinins is not yet very clearly understood. It has been shown by Bordet and others, however, that it is not the agglutinin that agglutinates, but that there is formed a complex of antigen and agglutinin which under proper physicochemical conditions of reaction and salt content permits the agglutinin to perform a purely secondary action of agglutination.

The specific character of the agglutination reaction has led to its use in determining the nature of many infections, the serum of the infected individual being used with cultures of known microorganisms. On the other hand, the test is often useful in determining the specific character of closely related microorganisms and their variations.[1]

PRECIPITATING SUBSTANCES.

Precipitins.—There is still another way in which the body reveals adaptive alterations in the presence of foreign protein substances. If a few cubic centimeters of the *blood-serum or exudate containing globulin* from one animal be injected into the subcutaneous tissue or peritoneal cavity of another species in repeated doses, it is found that, on adding a little of the blood-serum of the adapted animal to a dilution of the fluid injected, a precipitate is formed. This reaction is also specific, save that in some instances body fluids from closely related species, such as man and monkey, fowl and pigeon, sheep and goat, horse and ass, dog and fox, may both afford a precipitate. But this precipitate is invariably much more marked in the fluid used for adaptation than in the similar fluid from the related species.

[1] See, for agglutination tests in classification, *Park*, Jour. Infect. Dis., Suppl. No. 2, Feb., 1906, p. 1.

This reaction is extremely delicate; and it has been possible to recognize human blood in a dilution of 1:50,000.

By the use of this test Nuttall, who has made very extensive observations, has been able to demonstrate in a most striking fashion phylogenetic relationships between animal species and groups of species, both warm and cold-blooded, which have an important bearing upon classification.[1]

The Precipitin Test in Forensic Medicine.—The use of this precipitation test has been urged in forensic medicine to reinforce the present unsatisfactory methods of distinguishing between human and other blood. For if one have a rabbit or other animal artificially adapted to human blood from which fresh serum can be secured (even the dissolved dried serum will answer), he has only to dissolve in a little salt solution a suspected blood-clot, and, mixing the two, observe the result. If, under suitable conditions of dilution, cloudiness develops within a short time or if a precipitate be formed, it is claimed that the suspected material could have been derived from no other animal than man. Since, however, it has been found that the blood not only of monkeys but of some other of the lower animals may give slight precipitates under these conditions, and since other human fluids containing albuminous substances, such as saliva, pus, inflammatory exudates, etc., may also give precipitates, it is evident that the result of this test should be interpreted with great caution.[2] (See technique of precipitin test, page 228.)

The *white of a hen's egg*, injected into the peritoneum of a rabbit, after a time gives rise to substances in the rabbit's serum which induce a precipitate in fresh solution of hen's egg albumen. No precipitate is produced by this serum in albumin solutions from the blood of the mammalia, and only a slight precipitate is formed in the egg albumen of related fowls, such as the duck, for example.

By the adaptation of the living animal to extracts of *muscle* tissue from another species, precipitating substances may be formed in the serum which are specific for the muscle used in the injection and may be employed in the detection of food substitutions.

Milk of one animal thus introduced into the body of another gives rise to a substance in the adapted animal which causes a precipitate in the diluted milk used for injection, but not in the milk of another species, save sometimes in slight degree in milk from closely allied animals.

This reaction is also applicable to *plant albumins*. Thus, if an animal be adapted to a given species of *bacteria*, its blood-serum, on being added to the clear filtrate of the pure culture, throws down a precipitate which is in some instances light, in others voluminous. This reaction is again specific, except within the group limits of related species. Thus, it has been shown[3] that precipitating substances which are developed by the adaptation of the rabbit to the typhoid bacillus induce a slight pre-

[1] See *Nuttall*, Blood Immunity and Blood Relationship, Cambridge, 1904.

[2] For a study of the precipitation test for blood, see *Graham-Smith*, Jour. Hyg., London, 1903, iii, 269 (bibl.); also *Ewing* and *Strauss*, New York Med. News, 1903, lxxxiii, 871 (bibl.); also *Nuttall*, Blood Immunity and Blood Relationship, Cambridge, 1904. For the suggestion of a method of differentiating bloods by an hemolysis test, see *Neisser* and *Sachs*, Berl. klin. Wchnschr., 1905, xlii, 1388. For a discussion of the medicolegal value of the test, see *Hunt, E. L.*, Boston Med. and Surg. Jour., 1917, clxxvi, 48. For a general review, see *Hektoen, L.*, Jour. Am. Med. Assn., 1918, lxx, 1273.

[3] *Norris*, Jour. Infect. Dis., 1904, i, 463.

cipitate in the culture filtrate of the colon bacillus, but not in the filtrate of B. prodigiosus, for example.

Numerous experiments have shown that other vegetable albumins call forth specific adaptive precipitins.

This precipitation test is so delicate that it appears possible not only to distinguish the albumins from different animal and vegetable species, but to differentiate also some at least of the various albuminous substances in the individual.

Antiprecipitin.—Finally, it is worthy of note that it has been possible, by the adaptation of a fresh animal of the appropriate species to these precipitating sera, to obtain "antibodies;" in the case of milk adaptation, for example, by the use of the so-called lactoserum, to secure an antilactoserum capable, when added to the test fluids, of preventing the formation of the specific precipitate.

Nature of Precipitin.—A great deal of most careful research has been devoted to the nature of the precipitating substances which the scope of this book does not permit us to touch upon. But it should be said that in their resistance to heat and in other ways the precipitating substances appear to be more closely related to agglutinating than to lytic substances. It has been shown that the specific serum precipitates are capable of fixing complement and removing it from solutions as immune substances may be fixed and removed—red blood-cells for example—by the specific elements which incite their formation (see page 205).[1]

The Adaptive Bodies not Permanent.—The effects of foreign cells and their derivatives upon whatever body-cells produce the lytic, agglutinating, and precipitating substances, are apparently not lasting, since if the injections be suspended they gradually disappear from the serum. The time of their disappearance, however, like that of appearance, is not regularly the same, even in the same animal.

OPSONIC SUBSTANCES—OPSONINS.

The importance of phagocytosis among the agencies protective against microorganisms has been for some time fully recognized and many facts are known about their ingestion and intracellular destruction. But the exact processes by which this is secured and the effects of natural and artificial immunization upon phagocytosis are still obscure. It has been assumed that the protective substances in the plasma of immunized individuals stimulate the phagocytes to the ingestion and destruction of microorganisms, and so-called *stimulins* have been the subject of much discourse. It has been claimed that through the germicidal power of the serum, bacteria are killed and are then, more readily than when living, engulfed by phagocytes. But the existence of stimulins has not been demonstrated, and it is now well known that living as well as dead germs are ingested and destroyed by phagocytes. It has been assumed by many that the promotion of phagocytosis by immune sera

[1] See *Gay*, Centralbl. f. Bakteriol., Orig. I., 1905, xxxix, 603. This capacity of precipitates to fix complement has an important bearing on the accuracy of the Wassermann and Noguchi tests.

is due to a sensitizing substance (*substance sensibilisatrice*) which by action on either the leucocytes or the bacteria changes a negative chemotaxis into a positive.

In 1904 Wright and Douglas,[1] by the use of methods suggested by Leishman,[2] discovered in normal human serum, and in larger amounts in the serum of persons who had been immunized to certain microorganisms, substances which when placed in contact with the specific bacteria are capable, without inducing appreciable morphological changes, of so modifying them that they are more readily taken up by polymorphonuclear leucocytes than are the bacteria which have not been subject to this preliminary treatment (see Fig. 118). These substances Wright and Douglas called *opsonins*.[3] The opsonins tested by these

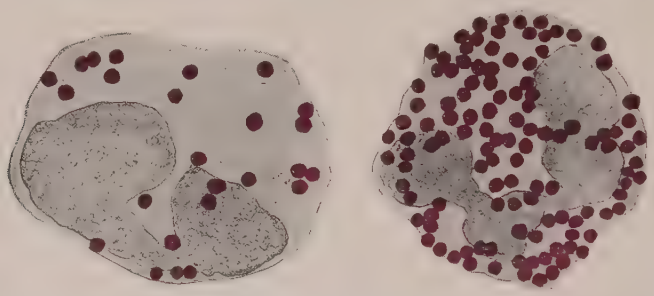


FIG. 118.—PHAGOCYTES, SHOWING THE EFFECT OF OPSONIC SUBSTANCES IN PREPARING BACTERIA FOR INGESTION BY LEUCOCYTES.

In the cell to the left the staphylococci were placed in contact with normal serum; in the cell to the right the cocci had been in contact with the serum of an animal artificially immunized to the microorganism. The cocci thus sensitized by the opsonic substances in the serum of the immunized animal have been taken up much more abundantly than those not thus prepared.

observers were found to be rendered inert by heating for half an hour at 60° C.; but later studies of others have shown that some opsonins—the opsonin of immune sera, for example—are more thermostable, resisting temperatures above 70° C. It was shown by suitable experiments that opsonins do not act upon the phagocytic cells, but only upon the bacteria.

Many studies of the serum of normal and immunized men and animals have been made by others since the announcement of Wright and Douglas. They are in general confirmatory and many new and interesting facts have been discovered relating to these protective substances —opsonins—present in the serum of normal individuals and markedly increased in the serum of those who have undergone natural or artificial immunization to special forms of bacteria.[4]

Neufeld and Rimpau[5] found in the serum of artificially immunized

[1] *Wright* and *Douglas*, Proc. Royal Soc., 1903, lxxii, 357; also ibid., 1904, lxxiii, 128.

[2] *Leishman*, Brit. Med. Jour., 1902, i, 73.

[3] From the Latin *opsono*, I prepare food for.

[4] The substance or substances which Wright and Douglas called *opsonins* had apparently been previously described by Metchnikoff as *fixateurs*, of which there seem to be two forms, bacteriolytic and phagocytic; see *Löhlein*, Ann. Inst. Pasteur, 1906, xx, 939.

[5] *Neufeld* and *Rimpau*, Deutsch. med. Wchnschr., 1904, xxx, 1458: also Ztschr. f. Hyg. u. Infectionskrankh., 1905, li, 283.

animals, substances acting not upon the phagocytic cells, but upon the bacteria in such ways as to promote their ingestion. These substances Neufeld and Rimpau called *bacteriotropic* in distinction to bacteriolytic substances sometimes formed in immunization, but they are apparently identical with opsonins.

It has been shown by Hektoen and Ruediger[1] that the opsonins in serum and plasma resemble toxins in that they apparently have toxophorous and haptophorous molecular groups (see page 199), by which, on the one hand, they secure union with the bacteria, and, on the other, effect changes in these organisms which render them susceptible to phagocytosis.

The opsonic substances occurring normally or developing in immune serum are capable of preparing not only bacteria, but other formed elements as well, red blood-cells, for example, for cell ingestion.[2] Substances opsonic for red blood-cells have been called *hemopsonins* or *erythrocyto-opsonins*, in distinction to the *bacterio-opsonins*. The relationship of opsonins to other immune substances—amboceptors and agglutinins—formed in similar adaptive processes is not yet clear, but they appear to be distinct.

Phagocytosis of red blood-corpuscles by endothelial and other cells in the lymph-nodes, bone-marrow, spleen, etc., is common in various infections, notably in typhoid fever (see page 276), as well as in toxic and anemic conditions.

Hektoen[3] found that normal serum may contain opsonins for heterologous as well as homologous erythrocytes, and that the adaptation of animals to alien blood commonly gives rise to the accumulation of hemopsonins in the blood. He showed, furthermore, that leucocytes in varying degrees may be phagocytic for opsonized red blood-cells. An interesting example of spontaneous phagocytosis by leucocytes has been noted occurring after direct transfusion in a case of pernicious anemia.[4]

Opsonins of immune sera appear to be specific, each uniting only with the formed elements under whose influence the special adaptation is secured. In this union—called "fixation" of the opsonin—the formed elements—bacteria or red blood-cells—are said to be *sensitized*, and from a serum containing several specific opsonins each can in turn be removed by fixation to its special cells and the separation of these by centrifugalization, just as specific amboceptors may be separated from hemolytic or bacteriolytic sera. (See page 205.)

The nature of the alterations which bacteria and other cells undergo by their union with opsonins is not understood. The bacteria are not killed or their capacity for growth diminished by it. The opsonins of immune sera of the lower animals sensitize bacteria and erythrocytes to human leucocytes, and *vice versa*. Thus the leucocytes of animals

[1] *Hektoen*, Jour. Infect. Dis., 1906, iii, 721.
[2] *Neufeld* and *Töpfer*, Centralbl. f. Bakteriol., Orig. I., 1905, xxxviii, 456.
[3] *Hektoen, L.*, Jour. Infect. Dis., 1906, iii, 434.
[4] *Hopkins, J. G.*, Arch. Int. Med., 1910, vi, 270.

as well as those of man may be used in the determination of the presence of opsonins in sera.

It is clear that opsonic action is of the highest importance in promoting phagocytosis. It is also evident from the numerous studies which have been made on the subject that in many instances this mode of destruction of bacteria by phagocytes is often effective under conditions in which extracellular bacteriolysis does not suffice for the protection of the infected individual.

The mere fact of phagocytosis, however, is not evidence of successful protection, since the ingested bacteria may destroy the phagocyte at once, may possibly gain in its interior by adaptation an exalted virulence, or may be transported to various parts of the body.

The virulence of bacteria has an important bearing upon the effectiveness of phagocytosis. It has been found that bacteria of high virulence are much less susceptible to phagocytosis than are the less virulent strains of the same species, both in normal and in immune sera. It would appear that virulent bacteria may be protected from phagocytosis both by their insusceptibility to opsonification and their capacity to produce substances harmful to the phagocytes.

In the light of our present knowledge of opsonins and their relations to phagocytosis, the occurrence of leucocytosis in various infections becomes of special significance. For if either a local or general leucocytosis be fostered hand in hand with the effective production of opsonins, the conditions would appear to be most favorable for the control of the infectious processes.

Clinical Significance of Opsonins.—The determination of changes in the opsonic power of the blood serum was thought by Wright and his followers to be of great practical importance as a guide to the administration of immunizing substances in the treatment of certain forms of infection. For a rise in the opsonic content marks, in accordance with this view, the successful development of those protective substances in the body which, by uniting with the bacteria, favor phagocytosis. If, on the other hand, after the administration of immunizing substances, the opsonic power falls, as is sometimes the case, and continues low, the indication is for a reduction or suspension of the dosage.

Remarkable curative results are recorded as the result of the administration of sterilized and standardized suspensions of the dead bodies of Staphylococcus pyogenes aureus in chronic furunculosis, and of the tubercle bacillus in tuberculosis, especially in its local phases, as well as other infections. The greatest value seems to lie in the prophylactic inoculation against typhoid and paratyphoid fevers, and against dysentery and cholera. The dead bodies of bacteria used in this way are called by Wright and his followers "vaccines."[1]

[1] This use of the word vaccine is not altogether to be commended, since the analogy between these substances and those used in the traditional vaccination for smallpox is not close. For a summary of the methods of preparing vaccine, see *Hiss* and *Zinsser*, Text-book of Bacteriology, 4th ed., New York, 1918; and *Kolmer*, Infection, Immunity, and Specific Therapy, 2d ed., Philadelphia, 1917. For an interpretation of present-day uses of vaccines, see *Theobald Smith*, Jour. Am. Med. Assn., 1913, lx, 1591.

Opsonic Power and its Determination.—Studies of the effects of opsonins upon bacteria as marked by phagocytosis are readily made outside the body. The simplest form of observation may be made by mixing equal parts of defibrinated blood and a suspension of a bacterial culture in 0.85 per cent. solution of sodium chloride, keeping this for fifteen to twenty minutes at 37° C., staining smears made upon a slide, and then determining the average number of bacteria found in the polymorphonuclear leucocytes. Since, however, under these conditions, the leucocytes are too few to obtain readily the averages of a large number, it has been found desirable for most purposes to concentrate the leucocytes by the centrifuge. The blood is diluted as it is drawn with a solution of sodium citrate 1.0 per cent. in 0.85 per cent. solution of sodium chloride. This prevents coagulation, and the performances of living leucocytes are not interfered with. This dilution can be effected by drawing blood from the finger tip into small glass capsules (Fig. 119) containing the sodium-citrate solution. This blood dilution may now be centrifugalized, and the leucocytes, which take a place above the red cells, may be drawn off by a pipette, washed with salt solution, and centrifugalized twice to remove the citrate, and then mixed with the bacterial suspensions and with the serum to be tested. This mixture is incubated for fifteen to twenty minutes; the smears are stained by the Jenner method (see page 534).

Fig. 119.—Glass Capsule for Drawing a Small Amount of Blood from the Finger Tip. As suggested by Wright.

In comparative studies it is necessary to free the leucocytes from their own serum by repeated washing in salt solution with centrifugalization, before testing their phagocytic power with bacteria exposed to an heterologous serum. Such washed leucocytes are found to be incapable of ingesting many forms of bacteria.[1]

Opsonic Index.—If the phagocytic count obtained with the use of the serum of normal man be considered as the unit, the proportion which the phagocytic count of the special serum bears to the unit is called the *opsonic index*.[2]

The determination of the opsonic power of sera in routine practice has been almost entirely abandoned owing to the laboriousness of the technique and the possibility of error in making the counts. The use of "vaccines" of dead bacilli is now very extensive, and the practice has to a large extent become standardized as to dosage and time intervals for injection. Part of the therapeutic effect in many chronic conditions is undoubtedly due to nonspecific protein reactions.

Although we have considered separately the development in the body of cytolytic, agglutinating, precipitating, and opsonic substances, it should be remembered that these may be and often are formed together in the same animal.

[1] For an excellent summary of phagocytosis and opsonins, see *Hektoen*, Jour. Am. Med. Assn., 1906, xlvi, 1407. For bibl. and summary of opsonins, see *Potter*, *Ditman*, and *Bradley*, Jour. Am. Med. Assn., 1906, xlvii, 1722, 1798. Also see *Wright*, Studies on Immunization, London, 1909.

[2] In his studies upon opsonins Wright has devised many delicate and clever technical procedures for collecting, measuring, standardizing, and mixing the various elements involved in the reactions, and with these the worker in the field should make himself familiar. See *Wright, A. E.*, Technique of the Tea and Capillary Tube, London, 1912.

LEUCOCYTE EXTRACT.

We have seen that the phagocytes, particularly the polymorphonuclears, are possessed of very subtle and, in the aggregate, very powerful capacities for bacterial cell destruction, both in their interior and through the substances which they may furnish to the body fluids.

It is apparent that, in the complex series of adaptations to one another in infection of the body-cells on the one hand and the microorganisms on the other, the balance must often be very nice in this muster of opposing forces.

Hiss proposed,[1] therefore, that the overtaxed or threatened phagocytes might be aided in an emergency if an extract of cells of their own kind in diffusible form such as might be secured by a sterile emulsion of dead cells were introduced into the body. He prepared such extracts and they have been administered both to men and to animals in divers infections with benefit in some cases. Cases of cerebrospinal meningitis, lobar pneumonia, and staphylococcus and streptococcus infection have been thus treated; and in experimental animals the infective processes induced by the pyogenic bacteria, meningococcus, typhoid and dysentery bacilli, and others have been markedly modified. It is now regarded as probable that such effects are due not, as was originally thought, to the neutralization of the bacterial poisons, but to the leucocytosis induced by a non-specific chemotactic reaction, following the injection of foreign protein.

Preparation of Leucocyte Extracts.—Exudates which contain a large proportion of leucocytes are secured from rabbits by intrapleural injection of sterilized aleuronat (page 229). After twenty-four hours the copious exudate is withdrawn, and the cells are separated by the centrifuge. These cells are extracted with sterile distilled water and after careful control as to the freedom from bacteria of the final emulsion, this is introduced beneath the skin.[2]

FIXATION OF COMPLEMENT.

We have seen when considering hemolysis (page 203), that when hemolytic serum which contains amboceptors is heated to destroy its complement, the amboceptor, if placed in contact with the species of red blood-cells to which it has been adapted, unites with them. Such blood cells are said to be "sensitized," because if now a small amount of complement in the form of fresh normal serum, "activating serum," be added, hemolysis takes place.

Similarly when heated bacteriolytic amboceptor in the form of an immune serum is added to its homologous bacteria—antigens—the latter are sensitized and are thus capable of absorbing and using up complement if fresh normal serum be added.

This delicate hemolytic reaction several years ago was made the basis of an ingenious method of testing for the presence of immune body by Bordet and Gengou.[3] The Bordet-Gengou test has been characterized as the method of *fixation of complement* for reasons which will be made clear through an example, as follows:

If one take bacteriolytic amboceptor in the form of, say, heated typhoid immune serum and add to this, first, an emulsion of typhoid bacilli and, second, complement in the form of fresh normal serum, and allow these to stand for five hours, it is evident from what we have seen above that the complement, if this has been added in proper

[1] *Hiss* and *Zinsser*, Jour. Med. Research, 1908, N. S. xiv, 321.

[2] For a study of bactericidal substances in leucocyte extracts, see *Zinsser, H.*, Jour. Med. Research, 1910, N S. xvii, 397.

[3] *Bordet* and *Gengou*, Ann. de l'Inst. Pasteur, 1901, xv, 129.

proportion, will have been all absorbed in the bacteriolytic reaction between itself, the amboceptor, and the typhoid bacilli. So that if we now add sensitized red blood cells, *i.e.*, heated hemolytic serum and red blood-cells, no hemolysis will take place because the complement necessary for this was previously absorbed, that is "fixed," in the bacteriolytic reaction.

That this is actually the case may be shown by replacing in the above experiment the heated typhoid immune serum by heated normal serum. In this case on the addition of the sensitized red blood-cells hemolysis occurs.

This method assumes that in the activating serum the hemolytic and bacteriolytic complement are identical at least in their combining capacities.

This "fixation of complement" has been brought more recently into practical use in testing for immune bodies in diagnosis (the Wassermann reaction), as well as in the determination of bacterial species and in the differentiation of proteins.

ALLERGY AND ANAPHYLAXIS.

Under the general term "allergy" are classed a number of complex phenomena of immunity, the name signifying an altered reactive quality of the body or the individual tissues. This changed reactivity may be due to previous disease or to the administration of foreign substances, as the injection of drugs or of horse serum, or to the occurrence of a disease like tuberculosis, which renders the body unusually susceptible to products of the tubercle bacillus. The altered reactivity of the body may express itself in three forms: 1, as an alteration in the speed of the reaction; 2, as an alteration in the amount of the reaction; and, 3, as an alteration in the quality of the reaction. Those substances which are capable of altering the reactive power of the organism are called allergins, which is a broader term than the word antigen, the latter being employed to designate those highly specific generators of immunity present in the proteins giving rise to antibody formation when placed in contact with the body cells. The term anaphylaxis is now being limited to that form of allergy due to the sensitizing of the body cells with some form of protein. The other form of allergy is due to substances which do not act as antigens but are, as a rule, well characterized chemical substances, as, for example, salvarsan, which sensitizes the tissue so that frequent doses may cause very severe reactions, or morphine, which acts less powerfully with each dose owing to the fact that the body cells ultimately develop a capacity to oxidize this alkaloid with greater activity than when administration is first begun.

The toxins of bacteria, such as the diphtheria and tubercle bacilli, may induce the production of antitoxins which neutralize the toxins or may sensitize the cells so that a second dose of the toxin may cause the death of the animal with symptoms of the disease which the particular toxin in question has the power to produce; for instance, a second dose of tetanus toxin may kill an animal with all the symptoms of tetanus. It is believed that the mechanism of death under these conditions is different from that which occurs in true anaphylaxis due to the introduction of a foreign protein into the circulation. If a dilute solution of tuberculin is dropped into the conjunctival sac of a person suffering from tuberculosis, there occurs a violent inflammatory reaction which is allergic in nature. The classic example of true anaphylaxis is that which

follows the spaced injection of foreign protein. If, for example, a guinea-pig is inoculated with a small quantity of horse serum and then seven to eleven days afterward a second injection is given, the animal often dies in a few minutes with symptoms of dyspnea, convulsions, involuntary defecation and urination, and fall of temperature. If the animal does not die it is immune and does not react to further injections of the same serum. If the second injection is made within a few days after the first no anaphylactic symptoms are produced nor can they ever afterward be produced by large or small doses. This anaphylactic condition can be transferred by injection into other animals of blood from an animal potentially anaphylactic. The condition may also be transmitted from mother to child, irrespective of whether the mother was rendered hypersusceptible before or after the beginning of pregnancy; it is not, however, transmitted in the milk.

Numerous theories have been proposed to explain this phenomenon. von Pirquet and Schick[1] thought that the reaction was a simple one between antigen and antibody, with the setting free of a product whose action on the remnants of the antigen still circulating in the blood caused the disturbance. Wolff-Eisner[2] believed that the first injection produced a ferment from the cells, capable of splitting the foreign protein injected, and that when this protein was injected a second time it was split rapidly, one of the split products being toxic. This theory, according to which the reaction takes place in the blood, received a good deal of support from the work of Vaughan.[3] Gay and Southard[4] suggested that a portion of the protein introduced in the first injection is assimilated by the cells, but that a fraction which is not digestible remains in the circulation and renders the tissue cells abnormally sensitive to reinjections of the same form of protein. The toxic nonassimilable substance, they called anaphylactin. Besredka[5] held that the antigen and the substance producing anaphylaxis are different. His theory was that the sensitizing protein contained an active element which gave rise in the injected animal to a specific antibody, which was circulated in the blood and stored up in the cells of the central nervous system; and that on a second injection a reaction took place between the specific antibody and a third substance present in the protein, which acted upon the nerve cells and gave rise to the symptoms. Doerr and Russ[6] regarded anaphylactic shock as an intracellular precipitin reaction.[7] Weil[8] believed that anaphylaxis is due to a reaction

[1] *v. Pirquet* and *Schick*, Die Serumkrankheit, Vienna, 1905; for a complete review with bibl. to 1910, see *v. Pirquet*, Arch. Int. Med., 1911, vii, 259, 383.

[2] *Wolff-Eisner*, Centralbl. f. Bakteriol., Orig., I., 1904, xxxvii, 350, 566, 684; and Berl. klin. Wchnschr., 1904, xli, 1105, 1131, 1156.

[3] *Vaughan*, Protein Split Products in Relation to Immunity and Disease, Philadelphia, 1913.

[4] *Gay* and *Southard*, Jour. Med. Research, 1907, N. S. xi, 143.

[5] *Besredka*, Compt. rend. Soc. de. biol., 1907, lxiii, 294; also *Besredka* and *Steinhardt*, Ann. de l'Inst. Pasteur, 1907, xxi, 384; and *Besredka*, Anaphylaxie et antianaphylaxie, Paris, 1917.

[6] *Doerr* and *Russ*, Ztschr. f. Immunitätsforsch., 1911, Orig., 1909, iii, 181.

[7] For an extensive review of the facts leading to the humoral theory of anaphylaxis, see *Friedemann*, Jahresb. ü. d. Ergebn. d. Immunitätsforschung, 1901, vi, 31; and Ztschr. f. Immunitätsforschung, Orig., 1909, ii, 591; and *Rosenau* and *Anderson*, Arch. Int. Med., 1909, iii, 519 (bibl.). For the views of *Richet*, who did much of the pioneer work on this subject, see L'anaphylaxie, Paris, 1912. See also review by *Doerr*, Kolle and Wassermann, Handbuch. d. path. Mikroorganismen, 2d ed., 1913, ii, 947 (bibl.).

[8] *Weil, R.*, Jour. Med. Research, 1913, N. S., xxii, 497.

between specific antibodies present in the cells and the introduced antigen, and that when passive sensitization is produced by the introduction of the blood of an anaphylactic animal, the body cells of the recipient absorb the introduced antibodies from the blood, and the cells thus become anaphylactically sensitive. This takes a certain time, usually twenty-four hours, at the end of which the animal can be killed by a single dose of antigen, because it has in its circulation an insufficient amount of antibody to protect the cells from the toxic effects of the introduced antigen or its split products. Weil held that an immunized animal is potentially anaphylactic but is protected by the immune bodies in the circulation, and that the difference between immunity and anaphylaxis lies solely in the fact that in the former the antibodies predominate in the serum, while in the latter they predominate in the cells, the cells being thus left unprotected.

This limited sketch of a few of the views on anaphylaxis is necessarily incomplete, since it is impossible in a work of this sort to do more than refer the student to larger treatises. Many of the observed phenomena do not fit any of the hypotheses. For instance, it is not clear why anaphylaxis should be prevented by placing the animal under the influence of chloral hydrate,[1] while morphine does not have this effect. Auer and Lewis,[2] having shown that the rapid death is due to asphyxiation induced by tetanic contraction of the smooth muscles of the bronchioles, showed also that atropine will prevent anaphylactic death. It must be remembered, also, that typical anaphylaxis to sera is seen chiefly in the guinea-pig. Other animals react quite differently to horse serum and may not be sensitive, though highly sensitive to other proteins. It is evident that our knowledge of this subject is still imperfect in spite of the enormous amount of investigation which has been carried out in the last ten years.

This much, however, is clear. The work of Longcope[3] has shown that the anaphylatoxin, whatever its nature, is destructive in its action upon the liver, kidney, and myocardium; and the part played by the liver has been emphasized by more recent studies.[4] It is now believed that some of the effects of the invasion of the system by bacteria, previously ascribed to endotoxins, may be rather a prolonged or chronic anaphylaxis produced by splitting of the bacterial proteins and setting free of a toxic moiety. It is probable, also, that the anaphylactic phenomena form the pathological basis of many hitherto but little understood and uncorrelated entities such as asthma, hay fever, eczema, and food intoxications. The frequence of a moderate eosinophilia in these conditions and also in experimental anaphylaxis is of interest. Food intoxications or susceptibilities have been much studied of late[5] and tests have been worked

[1] *Banzhaf* and *Famulener*, Jour. Infect. Dis., 1910, vii, 577.

[2] *Auer* and *Lewis*, Jour. Exper. Med., 1910, xii, 151.

[3] *Longcope*, Jour. Exper. Med., 1913, xviii, 678; 1915, xxii, 793; *Boughton*, Jour. Immunol., 1916, i, 105.

[4] *Weil*, Jour. Immunol., 1917, ii, 525 and 571.

[5] For a review of the subject see *Longcope*, Am. Jour. Med. Sc., 1916, cli, 625; also *Talbot*, Boston Med. and Surg. Jour., 1914, clxxi, 708; and *Blackfan*, Am. Jour. Dis. Children, 1916, xi, 441.

out to demonstrate the type of protein causing the reaction. This is most often egg albumen, and the inoculation of a scratch in the epidermis with a dilute solution of egg albumen will give rise to a sharp inflammatory reaction in a sensitive person. The intracuticular injection of a minute quantity of the same protein will produce similar effects; but great care must be observed, as almost instantaneous death has occurred following the use of less than half a cubic centimeter of egg albumen by this method. By careful treatment many of these persons can be immunized against the protein to which they are sensitive.

Of the diagnostic reactions the tuberculin, luetin, and mallein tests are anaphylactic in nature; the Schick test is not.

THE ABDERHALDEN REACTION.

It was thought by Abderhalden[1] that the introduction into the blood stream of a foreign protein of any type would incite the formation of a specific ferment which would act upon this protein primarily, and not be generally potent. On this assumption, he based a very delicate procedure for determining the presence of the cleavage products of the protein. One method was the detection of the alpha-amino-acids produced, by means of a substance known as ninhydrin. The blood-serum was allowed to act upon a carefully prepared substrate of the protein which the specific ferment was supposed to attack, as, for example, carcinoma tissue or placental tissue, and after digestion had gone on for a certain length of time, care having been taken to exclude bacterial action, the fluid was subjected to dialysis, and the dialysate tested. Another method was to determine the change in the optical rotation which occurred under the influence of the ferment.

While it is perfectly true that the injection of a foreign protein into the blood does alter that fluid, so that when serum from the recipient acts upon the antigen minute quantities of the products of protein cleavage are formed, there is no question, also, but that such digestion may be produced, though usually not to the same extent, by the use of normal sera.[2] For these reasons it has been believed that the digestion is accomplished by the enzymes normally present in the serum, rather than by any new-formed ferment; and as the studies of the most careful workers have not confirmed the claims of Abderhalden and his school, the diagnostic value of the procedure is extremely doubtful.[3]

The Bearing of the New Studies on Serum Therapy.—We have seen in an earlier section that the use of the blood-serum of animals immunized against pathogenic microorganisms for protective purposes in man has

[1] *Abderhalden*, Abwehrfermente, 4th ed., Berlin, 1914; and for a later review, Cor.-Bl. f. schweiz Aerzte, 1917, xlvii, 1745.

[2] *Bronfenbrenner*, Jour. Lab. and Clin. Med., 1915, i, 79; *Smith* and *Cook*, Jour. Infect. Dis., 1916, xviii, 14.

[3] For further information, see *Wells*, Chemical Pathology, 4th ed., Philadelphia, 1920; *Elsesser, O. J.*, Jour. Infect. Dis., 1916, xix, 655; *Van Slyke*, Arch. Int. Med., 1917, xix, 56; and *Jobling, J. W.*, and *Petersen, W. F.*, Bull. Johns Hopkins Hosp., 1915, xxvi, 356.

For the view that Abderhalden's specific ferments are merely the ferments of the pancreas and the intestinal mucosa circulating in the blood, see *Boldyreff*, Quart. Jour. Exper. Physiol., 1916. x, 175.

been of practical value in but few instances, and these mainly in cases in which the protective action was antitoxic. Protective sera for pneumonia and typhoid, streptococcus septicemia, plague, tuberculosis, cholera, and many other infectious diseases whose chief toxic incitors seem to be endotoxins have been persistently tested and found to be for the most part of doubtful value in man. A serum available for one type of pneumococcus has, however, recently been found, as well as one effective against the toxin of Bacillus aërogenes capsulatus.

It is possible that the reason why the serum of an animal immunized against a given pathogenic microorganism is not protective is that neither this serum nor the body fluids of the individual into whom it is injected for protective ends contain sufficient or suitable complements.

We have seen in our review of hemolysis that hemolytic serum heated to 56° C. loses its lytic power owing to the destruction of the very labile complements. We have seen, further, that this power is restored by the addition of a little fresh serum from a normal animal; that is, serum containing complement. Now it has been found that this "reactivation" of the serum, as it is called, can often be brought about by the sera of various animals. Thus, for example, the serum of the guinea-pig adapted to the erythrocytes of the rabbit is lytic for these cells of the rabbit. If such serum be heated to 56° C. it is no longer lytic, the activities of the complement are destroyed; but the serum can be reactivated by a little fresh serum, not only from a normal rabbit, but from the goat and the rat. The serum of many other animals, however, is ineffective under these conditions. The reason for this, of course, in accordance with Ehrlich's hypothesis, is that the complements of the reactivating sera have combining capacity with the special amboceptors, and so can become effective, while in other sera, the linking of the complement to the red cells through the amboceptors being impossible, there can be no restoration of the lytic action.

It is not difficult to secure immune substances (amboceptors) by the adaptation of animals to various kinds of pathogenic bacteria. These may be formed in such abundance as to be out of proportion to the complements. But unless these immune substances, when injected into the body for protective purposes, either carry with them or find in the new environment an abundance and appropriate forms of complements, they are not wholly available in destroying bacteria. One of the great problems of the immediate future, then, so far as serum therapy is concerned, seems to be to secure suitable complements to act with immune substances if the former do not exist in the human fluids, or to reinforce these substances from the sera of suitable animals if the human stock be scanty. There is, however, much ground for believing that in order to be most effective the complements with which we may seek to reinforce the potency of bacteriolytic sera in man should come from species closely allied to him.

If the securing of an appropriate complement is thus of such importance in the attempt to prepare bacteriolytic sera for therapeutic purposes, the maintenance of sufficient complements in the human body must be

of the utmost significance in its intrinsic protective mechanism against infection. That this consideration is not without support in fact is shown by the studies of Abbott, Longcope, and others,[1] who have found that after the continuous administration of alcohol and in various chronic as well as acute diseases, the amount of complement in the blood may be notably reduced. We have thus a definite contribution to our knowledge of one of those factors in predisposition to infection which, in a general way, are so fully recognized, but which are, for the most part, but ill-defined and little understood.

But the securing of effective bactericidal and bacteriolytic agents would not in itself be a satisfactory solution of this urgent problem in serum therapy. One can readily conceive that complete success in this respect might be an added source of danger to the victim of infection. For in the case of those bacteria whose harmful effects in the body seem to arise largely through the setting free of endotoxins, it is probable that if these were not at once and properly combined or otherwise cared for, the wholesale destruction of the bacteria might prove a curse and not a blessing. And this, in effect, is the trend of modern thought. The diminution of complement in the serum of animals suffering from anaphylactic shock has been noted. In addition, the production of anaphylatoxins by the exposure of proteins or bacteria to the action of fresh complement-containing serum suggests that the real defense of the organism may not take place in the blood current so much as was originally thought by the Ehrlich school; and the tendency to-day is to look upon the leucocytes and fixed cells of the body rather than the antibodies of the plasma, as the ultimate resource against the invader.

The Specific Character of Artificial Immunization.—It is not yet possible to say in many cases to what extent the immunization effected in any of the various ways indicated above is specific. In some cases it appears to be so. That is to say, the protection which is afforded, for example, by an attack of diphtheria or by the gradually increased administration of the diphtheria toxin, or by the use of the immunizing serum, is limited to this particular disease, and is not to be secured, at least in such marked degree, by the use of other bacteria or bacterial products. In some instances, on the other hand, immunization against one microorganism or its toxins, or against special toxic substances, affords protection against infection or intoxication by entirely different agents. Thus animals may be immunized against anthrax by inoculation with Bacillus pyocyaneus. Again, in an animal adapted to typhoid bacilli, the intravenous injection of a non-specific proteose will incite a great enrichment of the blood with typhoid antibodies, apparently by direct stimulation of the hematopoietic system.[2]

It should be borne in mind, however much importance we may attach to the formation and action of the antitoxic substances, that these are not necessarily always present in either natural or acquired immunity to bacteria or their toxins. Tolerance to bacterial toxins may be established,

[1] For a study of this subject, see *Longcope*, Jour. Hyg., 1903, iii, 28.
[2] See, for further examples, *Gay*, Jour. Lab. and Clin. Med., 1915, i, 13.

as may tolerance to other kinds of poisons, without the intervention of antitoxic or other chemical agents.

The Complexity of the Processes Involved in Immunization.—It thus appears that while we know a great deal about the ability of the living body to protect itself against the incursions of microorganisms and the ravages of their poisons; while a field is opened for the study of artificial immunization which is of the highest promise, both for the advancement of science and for practical benefit to the victims of infectious disease; while illuminating and far-reaching hypotheses are current which account for many of the complex phenomena, we are yet very far from comprehending many of the details of the processes by which immunization is secured.

We do not know why the cells of certain animals or why different kinds of cells in the same animal are more susceptible than others to the presence of particular poisons; why, for example, the rabbit is less susceptible than man to morphine; why strychnine should affect the nerves while curare acts upon the muscles; why the common fowl should be extremely insusceptible to the tetanus toxin so powerful in many other animals. We are even ignorant as yet in most cases of either the chemical or structural changes in cells by which the deleterious action of poisons is effected. This is, indeed, not surprising when we reflect that the processes which are involved are of the most subtle and complex nature and that our knowledge of cell metabolism even under normal conditions is most crude and fragmentary, consisting largely in rather gross determinations of end-products and leaving out of the account the numberless molecular transformations and combinations through which the life processes of the cell are carried on.

The living body-cell is very nicely adapted to its normal environment; the living bacterium is almost equally sensitive to the conditions under which its metabolism takes place. Thus it is that, when these subtle organisms react upon each other, we are wholly unable with our present knowledge to follow the steps by which the more gross manifestations of disturbance which we call disease are reached.

But there seems to be abundant ground for the belief that the protective agencies which are evoked in both natural and artificial immunization are simply those which the body makes use of in its normal metabolism, exaggerated and diverted to different ends, it is true, in the face of emergencies and the establishment of new cell environments, but giving evidence of the birth of no new physiological capacities.[1]

[1] The hypothesis of Ehrlich, which so closely correlates the action of toxins with the assimilation of nutrient stuff, has led to new conceptions of the details of the relationship of foods transformed by the preliminary digestive process to the material which is finally placed at the disposal of the cells. It seems not unlikely not only that through the action of the cell receptors the food material which arrives in the body fluids may be adapted to the specific uses of the cells, but that by the formation of countless varieties of substances analogous to the so-called "antibodies" of immunization, the cells are protected against equally various toxic substances. It this be true, the hope seems justified that, following the lines of research suggested by this new technique, we may be able ultimately to understand more clearly the details of the so-called internal secretion and those disturbances of chemical adjustment which give rise to many important phases of autointoxication.

Technique.

Agglutination Tests.

For Microorganisms.—The serum to be tested is mixed in the proportion of 1 c.c. to 9 c.c. with 0.85 per cent. sodium chloride solution, making a dilution of 1:10, and cleared from red corpuscles if necessary, by filtration. From this solution various dilutions are prepared in a diminishing series, 1:20, 1:50, 1:100, etc. These solutions may be put into slender test-tubes, and to each is added an equal quantity of a suspension in a 0.85 per cent. NaCl solution of a twenty-four-hour-old agar culture of the microorganism to be tested.

To secure these suspensions add 5 to 10 c.c. of the salt solution to the culture, distribute with a platinum needle, allow the larger lumps of culture to settle, and pipette off the turbid supernatant portion. This suspension of the culture in 0.85 per cent. salt solution is now mixed with the diluted serum to obtain the requisite proportions. Thus, 1 c.c. of the 1:10 serum mixed with 1 c.c. of the suspension gives a 1:20 dilution; 1 c.c. of the 1:10 serum with 2 c.c. of the suspension, a 1:30 dilution. These suspensions of the culture in the series of tubes of diluted serum are now kept for from one to twenty-four hours at 37° C. The clumps of bacteria when agglutination has taken place may be seen by a hand glass. The clumps oftentimes sink in the tube and the fluid becomes clear. Microscopic study of agglutination is made by mixing the diluted serum and the bacterial emulsion on a cover-glass which is then inverted on a hollow glass slide and sealed with vaseline. For special and for diagnostic purposes more exact methods are required, for which see works on bacteriology or on clinical diagnosis.[1]

For Blood-cells.—A demonstration of the agglutinability of red blood-cells may be made by adding to a 5 per cent. dilution of defibrinated blood in 0.85 per cent. salt solution, a small quantity of an aqueous emulsion of ricin. The blood-cells soon clump and settle, leaving the fluid clear and colorless.

Precipitin Test.

While the precipitin or so-called biological test for human blood has been suggested and used in medicolegal cases of importance, its limitations are not yet fully determined and one should not enter upon its practical applications in cases of importance without large experience of the method and the possibilities of error.[2]

For demonstrative purposes, however, the technique is simple. A fragment of blood-clot to be tested as to its human origin is dissolved in a small quantity of 0.85 per cent. salt solution and passed through filter paper to secure a clear fluid. To this solution in a test-tube is added about twice the quantity of the serum of a rabbit or guinea-pig which has been injected with successive doses of human serum. This adaptive serum should have been tested with a known human serum to insure its reliability. Control tubes should be made containing mixtures of the several ingredients used, without the clot solution to be tested. The tubes are now all kept for one hour at 37° C., when if the suspected clot is of human blood the tube which contains it will show a precipitate while the controls will remain clear. The characteristic precipitate should soon settle in the tubes, leaving the fluid clear.

Hemolysis Tests.

In comparative observations on hemolysis it is convenient to make a 5 per cent. dilution of defibrinated blood with 0.85 per cent. salt solution. One may use narrow test-tubes, 5 mm. in diameter, putting into a series of these 1 c.c. of the diluted blood, adding to each the serum or other hemolytic agent to be tested, and filling up with

[1] *Hiss* and *Zinsser*, Text-book of Bacteriology, 4th ed., New York, 1918, or *Wood*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917.

[2] For technical and other details of the precipitin test, see *Uhlenhuth* and *Weidanz*, Praktische Anleitung zur Ausführung des biologischen Eiweissdifferenzierungsverfahrens, Jena, 1909; *Leers*, Die forensische Blutuntersuchung, Berlin, 1910.

salt solution to, say, 2 or 2.5 c.c. The tubes are shaken and placed for an hour at 37° C., then in an icebox. A control tube of the blood in simple isotonic salt solution 0.85 per cent. should accompany each series. If the hemolytic serum is old complement must be added.

Following the suggestion of Wright, tests for hemolysis may be made in capillary tubes, each long tube containing several tests or dilutions by the intervention of a bubble of air between each segment of the mixed test fluid and diluted blood.

To Secure Sterile Inflammatory Exudate Containing Leucocytes and other Living cells.

It has been found that the injection of wheat gluten into the pleural cavity of rabbits or dogs induces an exudative inflammation, the exudate usually containing, at the end of twenty-four hours, many living leucocytes. Leucocytes secured in this way have been largely used in determining the chemical character of their cytoplasm, as well as for experiments on phagocytosis. The most convenient preparation is the so-called *aleuronat*, a mealy food preparation. A convenient method is to inject into the pleural cavity 10 c.c. of a suspension of aleuronat in starch water (aleuronat, 5 grams; starch, 1.5 grams; water, 100 c.c.). The exudate may be removed with a capillary pipette if small quantities only are required, or the animal may be sacrificed if larger quantities of the exudate are necessary.

Polymorphonuclear leucocytes may also be secured in considerable quantity by the injection of 10 grams of sterile bouillon into the peritoneum of the rabbit. The exudate is removed at the end of twenty-four hours.

To secure an exudate containing a preponderance of mononuclear cells one may inject into the peritoneum of the rabbit a solution containing 1 mgm. of pilocarpin, the exudate to be removed at the end of twenty-four hours.

The Study of Hemophagocytosis.

If the serum of rabbits adapted by successive injections into the peritoneum to the blood of guinea-pigs be injected into the peritoneal cavity of guinea-pigs, after a time the peritoneal fluid as well as the spleen and other blood-forming organs are found to contain various cells which have ingested the erythrocytes. The peritoneal fluid may be secured for examination at various intervals by a capillary tube inserted into the peritoneal cavity.

Hemophagocytosis in vitro may be studied by procedures similar to those employed in the study of bacteriophagocytosis. (See opsonins, p. 219.) The serum of an animal adapted to alien blood, if lytic, is deprived of this power by destroying the hemolytic complement by heating for half an hour at 60° C. A small portion, say, 0.1 c.c. of this serum, is now mixed with an equal quantity of a 5 per cent. suspension of washed red blood-cells in 0.85 per cent. salt solution. To this is added a small quantity of living leucocytes of man or of the guinea-pig or dog secured from citrated blood or, in animals, from fresh aleuronat exudates (see above), and the mixtures kept for an hour at 37° C. Smears are then made and stained with the Jenner or other double stain.[1]

To Collect Small Samples of Serum for Agglutinative, Precipitin, or Hemolysis Tests.

The suggestions of Wright are most helpful in the technique of serum collection in small quantities. The finger is constricted by the handkerchief or a bandage, not tightly enough to stop the blood flow, but enough to induce marked congestion; and the puncture is made by a needle or a fine-pointed glass. The drop of blood as it exudes is drawn into a small capsule of the form shown in Fig. 119, held so that it will act as a siphon. When partly filled, the ends are sealed, first the straight end; then as the air here cools, the blood will be drawn back from the capillary end, when this is closed. The tube is set slightly aslant for clotting, after which the serum may be secured in capillary pipettes by breaking off the straight end of the capsule after scratching it with a file.

[1] See *Hektoen*, Jour. Infect. Dis., 1906, iii, 434; also Jour. Am. Med. Assn., 1906, xlvi, 1407.

The Method of Adaptation of Animals to Alien Substances.

The adaptation, or immunization, as it is called, of animals to various alien substances, sera, red blood-cells, etc., in order to secure lytic agglutinating and precipitating substances, is readily accomplished. For general demonstration purposes the rabbit is well suited. The simplest method is that of intravenous injection. The external lower surface of the ear is shaved or the hair is removed with depilatory paste, and the skin is then disinfected with dilute lysol. The ear is warmed or rubbed so as to dilate the vein, and about 0.5 c.c. of washed corpuscles are injected into the vein from a sterile syringe, a fine needle being used so as to avoid bleeding after withdrawal; if this occurs, the edge of the ear may be clamped with a small clip or touched with tincture of ferric chloride. The injection is repeated once or twice at intervals of two days. At the end of ten days the ear vein is incised, and a few drops of blood are drawn into a Wright capsule; the blood is allowed to clot in the capsule; and the serum is secured. If large quantities of serum are desired, the animal may be bled to death, the blood being drawn into sterile receptacles by means of a glass cannula tied into the carotid artery. Only a certain proportion of animals will give good hemolytic or other sera. If a satisfactory result is not obtained in any instance, the animal should be discarded, and other animals inoculated. It is quite unnecessary to use larger quantities of blood than 1 c.c.

For agglutinative or bactericidal sera, a suspension of the bacillus against which the serum is desired should be made from an agar slant by pouring into a test-tube a few c.c. of a 0.85 salt solution, and emulsifying the bacteria by means of a platinum loop. A small amount of this emulsion, 0.1 or 0.2 c.c., is injected into an animal. If the organisms are those which kill the animal rapidly, they should first be killed by heating for a short time to 52° C. In order to obtain precipitating sera, the blood is allowed to coagulate and from 0.5 to 1.0 c.c. of the separated serum is used for the injection. It is often not necessary to repeat this injection, but if this must be done, the reinjection should be made within forty-eight hours.[1]

Bibliography on Studies of Immunity.

For an early admirable résumé of immunity, consult *Weigert*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1897, iv, 107; for a good later summary see *Müller*, Infection and Immunity, 1912. Consult also *Metchnikoff*, Immunity in Infectious Diseases, 1905, in which much lore is gathered and many ingenious points of view of the author are set forth. *Kolle* and *Wassermann's* Handbuch d. path. Mikroorganismen, 2d ed., 1912–13, contains excellent summaries of various phases of immunity; as does also in more compact form the Experimentelle Bakteriologie of *Kolle* and *Hetsch*, 3d ed., 1911. Many valuable reviews are contained in the Jahresb. ü. d. Ergebn. d. Immunitätsforschung, Stuttgart. See also *Kraus* and *Levaditi*, Technik u. Methodik d. Immunitätsforschung; *Much*, Immunitätswissenschaft, 2d ed., Jena, 1914, and *Pfeiffer*, Eiweissanaphylaxie, 1911.

The records of the researches just summarized in cytolysis and the application of Ehrlich's "side-chain" hypothesis are widely scattered through the German, French, and English technical periodicals. The most important of the studies of Ehrlich and his associates in this field are collected by *Ehrlich*, Gesammelte Arbeiten zur Immunitätsforschung, English Transl. by Bolduan, 2d ed., New York, 1910; see also *Bordet*, Studies in Immunity, translated by Gay, New York, 1909 and *Muir*, Studies in Immunity, London, 1909.

The summary of *Aschoff*, Die Seitenkettentheorie und ihre Anwendung auf die künstliche Immunizierungsprozesse, Ztschr. f. allg. Physiol., 1902, i, 3, is most complete and contains a full bibliography. The monograph of *v. Dungern*, Die Antikörper, 1903, contains much valuable material.

[1] For further details and many interesting data, consult *Nuttall*, Blood Immunity and Blood Relationship, London, 1904; *Kolle* and *Wassermann*, Handbuch d. path. Mikroorganismen, 2d ed., and *Kraus* and *Levaditi*, Handbuch d. Immunitätsforschung, 1914; and *Kolmer*, Infection, Immunity, and Specific Therapy, 2d ed., Philadelphia, 1917.

In English, the Huxley Lecture by *Welch* (Recent Studies of Immunity, Medical News, October 18, 1902) is admirable, and deals with especial fulness with toxins and their relationship to various important pathological processes.

Ritchie's discussion of the subject (Jour. Hyg., 1902, ii, Nos. 2, 3, and 4) treats in a clear and philosophical fashion the facts and hypotheses involved.

See also *Nuttall*, Blood Immunity and Blood Relationship, 1904; *Bolduan* and *Koopman*, Immune Sera, 5th ed., New York, 1917; and *Hektoen*, Résumé of Immunity, 1905.

For study of transmission of immunity to offspring see *Theobald Smith*, Jour. Med. Research, 1907, N. S. xi, 359.

For most recent reviews, see *Zinsser*, Infection and Resistance, 3rd ed., New York, 1923; and *Kolmer*, Infection, Immunity and Specific Therapy, 2d ed., Philadelphia, 1917.

For a study of the local specific therapy of infections see *Flexner*, Jour. Am. Med. Assn., 1913, lxi, 447, 1872.

CHAPTER IX.

THE INFECTIOUS DISEASES.

General Considerations.

In the study of the infectious diseases it is especially important to bear in mind that the abnormal processes through which the disturbances incited by microorganisms are manifested are processes of the body-cells and not processes of the microorganisms. The microorganisms do, indeed, incite the train of phenomena by which the disease is manifested, and the nature or "species" of the microorganisms may largely influence the character of the phenomena, but the stored-up energy which is released in this manifestation is body-cell energy and not that of microbic metabolism. The microbes are excitants of disease, but the disease is a performance of the body-cells. If these obvious considerations be held in view, it will be convenient, in considering certain of the infectious diseases, to use the familiar and much abused term "specific" as indicative of those phases of abnormal body-cell performance which are apt to occur in characteristic ways in response to special forms of microbic stimulus. Thus the poisonous substances which the tubercle bacillus builds up out of the organic material upon which it feeds are in part such as exert a peculiar influence upon connective-tissue cells, leading to their proliferation and the temporary formation of new tissue—the tubercle. This, together with associated action of the same or other metabolic products of the living bacillus, forms a group of lesions and disturbances which is characteristic of the action of the tubercle bacillus in the body. In this sense tuberculosis is a "specific" disease. On the other hand, the poisons eliminated by the tubercle bacillus may incite responses on the part of the body-cells which are practically identical with those which many other toxic substances, both of bacterial and of other origin, induce—fever, degeneration, etc. These manifestations of the action of the tubercle bacillus upon the living body-cells are not "specific."

In our study of the individual infectious diseases we shall encounter many examples of this variety in the effects which pathogenic bacteria induce—the more characteristic, on the one hand, and, on the other, the more general responses which the body-cells make to deleterious agents.

Classification of the Infectious Diseases.—It is common to group diseases from either the clinical or the morphological or the etiological standpoint. But a complete rational classification of disease is not at present possible, because in very few conditions have we even an approximately complete knowledge of the symptoms, the excitants, or the morphology of the lesions.

In the infectious diseases as we now define them, the excitant is definite and in many cases known, but a classification based upon the character of the excitants alone would be, as Martius has urged, a classification of the microorganisms and not a classification of the diseases. If every microorganism capable of exciting disease always met in the body a similar response, the matter would be comparatively simple. But the fact that the responses of the body-cells to bacterial invasion are exceedingly varied, and that dissimilar organisms may evoke similar responses, renders a simple etiological classification even of the infectious diseases unsatisfactory, if not impracticable. Thus it is that it is convenient to consider the infectious diseases in part together, in part in connection with the special organs in which their more common and characteristic lesions are manifested. Such a classification of the infectious diseases as is here made is based in part upon similarity of lesions, in part upon the relationships of the microorganisms concerned, and may wisely be regarded only as a convenient form of catalogue.

Groups of Bacterial Disease-Excitants.—One of the interesting results of the later studies of bacteria and their associations with the infectious diseases is the discovery that many microorganisms which have been proved to be excitants of disease in men or in lower animals are closely related to forms which are not pathogenic. So that we now recognize many bacterial groups which we are wont to characterize by the name of the pathogenic representative. Thus there are staphylococcus and streptococcus groups of closely similar organisms, most of them harmless to man. There is the colon-bacillus group, embracing many closely related forms difficult to identify. The tubercle-bacillus group, the diphtheria-bacillus group, the actinomyces or streptothrix group, are other examples of this relationship. The more these related forms are studied, the more evident it becomes that in very slight physiological variations may lie the difference between pathogenic and non-pathogenic forms, and that equally slight variations in the susceptibility of the host may be of corresponding significance.

In the arrangement and associations of the infectious diseases considered in this section, the existence of these bacterial groups will be frequently recognized.

SUPPURATIVE AND ALLIED FORMS OF INFLAMMATION.

We have seen in an earlier part of this book that in various kinds of injury in the living tissue there may be a series of responses on the part of the body-cells which constitute or give rise to the phenomena and lesions of inflammation. One of these forms of tissue response to injury is called *suppuration* or *suppurative inflammation.*

We have seen that the characteristic feature of suppurative inflammation is the collection, at or near the seat of injury, of leucocytes, mostly of the polymorphonuclear type. These leucocytes, attracted through chemotaxis, emigrate from the smaller vessels and gather in the tissues. Here through their phagocytic powers they may directly or indirectly de-

stroy living microorganisms; by lytic substances which they elaborate they may soften and remove dead tissue (see page 123); or they may themselves succumb to the action of poisons or other local conditions inimical to their life. While, to a limited extent, a suppurative inflammation can be incited by chemical agents, such as ammonia, turpentine, etc., in most cases it is incited and sustained by microorganisms or by poisons which these microorganisms set free as the result of their own metabolism or by the decomposition of substances in the tissues or the tissue fluids.

Before considering in detail the characteristics of the various forms of microorganisms which may act as excitants of suppurative inflammation, it is necessary for us to survey the various phases which this process presents under different conditions.

Phases of Suppurative Inflammation.—In the first place while the emigration, proliferation, and gathering of leucocytes are the most characteristic features in this form of inflammation, these are always associated with the accumulation of more or less fluid transudate from the blood-vessels and often with the formation of fibrin. These, the leucocytes, the serum, and the fibrin, constitute the *exudate*. Furthermore, associated with the accumulation of the exudate there may be albuminous degeneration and necrosis of cells and tissue of the affected part or of the formed elements of the exudate itself. Finally, a proliferation of the fixed cells of the affected region, connective-tissue cells, endothelium, etc., frequently accompanies the exudative phases of inflammation and may dominate the process when regeneration and repair are under way (see page 91).

Although the processes involved are essentially the same, it has been found convenient to attach special names to various topographic forms of suppurative inflammation, the differences depending largely upon the origin, situation, extent, and complications of the primary lesion, somewhat, however, upon the qualities, fixed or variable, of the infecting microorganism. Thus a suppurative inflammation involving the serous surfaces and resulting in the accumulation of a purulent exudate in the serous cavities, such as the pleural and the pericardial, is called *empyema*. An exudative inflammation of the mucous membranes with a marked emigration of leucocytes from the vessels of the submucosa is called a *purulent catarrh* or *blennorrhea*.

Pustules are superficial collections of purulent exudate in the skin.

Furuncle.—A *furuncle* is an acute, circumscribed, suppurative, and necrotic inflammation of the skin, the necrosis commonly involving a central plug or core. Furuncles are usually incited by Staphylococcus pyogenes aureus, rarely by Streptococcus pyogenes. They are common on the neck, back, buttocks, perineum, and axilla. Diabetes, marasmus, and obscure nutritional disturbances, often associated with worry and overwork, seem to predispose to this form of infection. The invasion of the staphylococcus is usually through the sebaceous glands and hair follicles. Furuncles may be experimentally induced by rubbing cultures of staphylococcus over the intact skin.

From the seat of infection the inflammation extends outward and in depth to a varying extent. The tissue becomes hard from infiltration of the tissue interstices with fluid and leucocytes, by the swelling of the stroma and connective-tissue cells (Fig. 120). The vessels are congested and the central portions become more or less necrotic, with gradual liquefaction of the tissue and the development of pus. Lymphangitis and hyperplasia of the associated lymph-nodes may accompany furuncles.

Carbuncle.—If the infection of several contiguous hair follicles, either immediately or in rapid succession, takes place, so that several centers of necrosis, with surrounding areas of exudative inflammation,

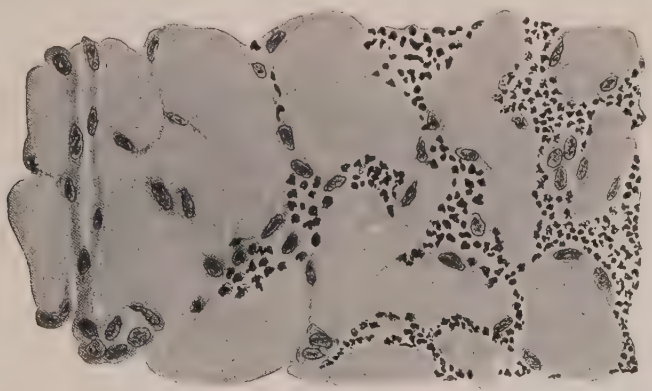


FIG. 120.—SECTION OF A BOIL—FURUNCLE. SHOWING THE RED AND SWOLLEN AREA.
On the left the connective-tissue cells are swollen and proliferated and the lymph-spaces are distended with fluid. Nearer the center of the boil the connective-tissue spaces are infiltrated with pus and the fibrils of the stroma swollen.

merge, the resulting lesion is called *carbuncle*. The process is essentially similar to that involved in furuncle, but usually more severe and extensive. Carbuncle is common on the neck, back, and face.

A diffuse infiltration of the subcutaneous or deep fibrous tissue, muscle tendon, periosteum, or of the interstitial tissue of the viscera, with exudate, is called *phlegmon*. If in this phlegmonous inflammation there be much serous fluid associated with the cell accumulation, as is commonly the case in the earlier stages of the process, the condition is often named *purulent edema*. When, on the other hand, there is a more or less circumscribed collection of purulent exudate in the depth of the tissues or organs, associated with necrosis and fluidification of the tissues involved, it is customary to call the result of the process an *abscess*

In some cases of exudative inflammation, particularly those involving the serous surfaces, the exudates often occur together in the most variable proportions; they are formed under the influence of the same agents, and frequently an exudate at first simply serous in character becomes fibrinous or purulent or both together.

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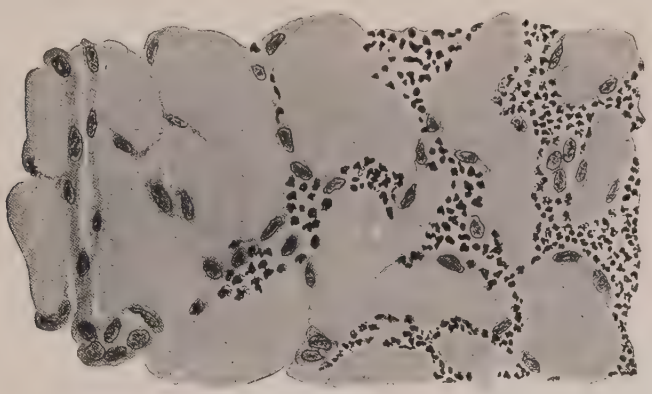

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In some cases of exudative inflammation, particularly those involving the serous surfaces, the exudates often occur together in the most variable proportions; they are formed under the influence of the same agents, and frequently an exudate at first simply serous in character becomes fibrinous or purulent or both together.

Of these alterations in the body, which are of frequent occurrence in many forms of toxemia, whether induced by bacterial or other kinds of poisons,[1] the only ones which demand special notice here are the *focal necroses*. These usually small, often sharply circumscribed areas of dead tissue[2] may be present in any of the viscera, but are often most abundant and conspicuous in the liver (Fig. 123). They vary considerably in appearance, depending upon the stage of the tissue involvement. The cells in the affected area may be swollen, the cytoplasm more transparent than normal, while the nuclei may remain unstained with the usual dyes or show various phases of fragmentation or disintegration; or they may disappear altogether. Again, the cells in the involved areas may become more coarsely granular than is normal, may undergo a change similar to that seen in coagulation necrosis, and with destruction of the nucleus may form deeply staining, irregular clumps or masses, or may disintegrate.

Associated with or following these changes there may be a gathering of leucocytes about and within these necrotic areas, so that the foci may present the appearance of little abscesses or masses of lymphoid tissue. Finally, these necrotic areas may undergo repair and be replaced by small, spheroidal, young connective-tissue cells, granulation tissue, or finally by small masses of cicatricial tissue.[3]

Septicemia and Pyemia.—Bacteria as well as their toxins may be distributed from a local portal of entry or an infected region throughout the body, not only inciting general functional and structural changes, but, when the bacteria lodge in various situations, giving rise by new local proliferation to fresh foci of inflammation.

It is customary to designate a pathological condition in which bacteria as well as their toxins are distributed through the body by the blood- and lymph-channels, as *septicemia*.[4] When fresh suppurative foci develop as the result of this distribution, the condition is called *pyemia*.

The terms *septicemia* and *pyemia* are survivals of a nomenclature adapted to the period before the nature of the excitants of infectious disease was definitely known. The manifestations of septicemia were then attributed to the presence of putrid material in the blood. *Pyemia* expressed the belief that the lesions characterizing this condition were due to the presence of pus in the blood. The term *bacteriemia* is sometimes and more correctly used to indicate the presence of bacteria in the

[1] See for effects of abrin and ricin intoxication, *Flexner, S.*, Jour. Exper. Med., 1897, ii, 197; also *Muller, F.*, Zieglers Beitr., 1900, xxvii, 331 (bibl.).

[2] It seems probable that this marked localization of the action of a soluble poison in the tissue fluids may be due to some local vulnerability or susceptibility induced, perhaps, by limited vascular disturbance or by nutritional defects otherwise induced. In some instances local necrotic foci may be due to agglutinative thrombi (see p. 37).

[3] For a comprehensive study of focal necrosis and other associated lesions in certain forms of toxemia consult the excellent study of *Flexner*, The Pathology of Toxalbumin Intoxication, Johns Hopkins Hosp. Rep., 1897, vi, 259 (bibl.).

[4] The mere presence of a moderate or even of a large number of bacteria in the blood does not of itself indicate septicemia, since the protective mechanism of the body suffices, under usual conditions, for the disposal of such an invasion. See discussion on page 182.

blood, but the old words with their new implications and limitations are still commonly employed.[1]

The term *pyemia*, as will be seen, indicates a clinical and anatomical phase of septicemia.

The new foci of suppuration in pyemia are called metastatic abscesses, and in distribution these may bear an obvious relationship to the seat of the primary lesion. Thus, in suppurative processes in the intestinal tract, metastatic abscesses are liable to occur in the liver. From suppurations in the skin, bones, muscles, etc., infectious emboli may be transmitted to the lungs and lead to infarction and abscess; or, passing these organs, the germs may induce multiple abscesses in the kidneys and in other viscera.

It should be remembered that the point of introduction into the body of the offending germs may be wholly concealed and not associated

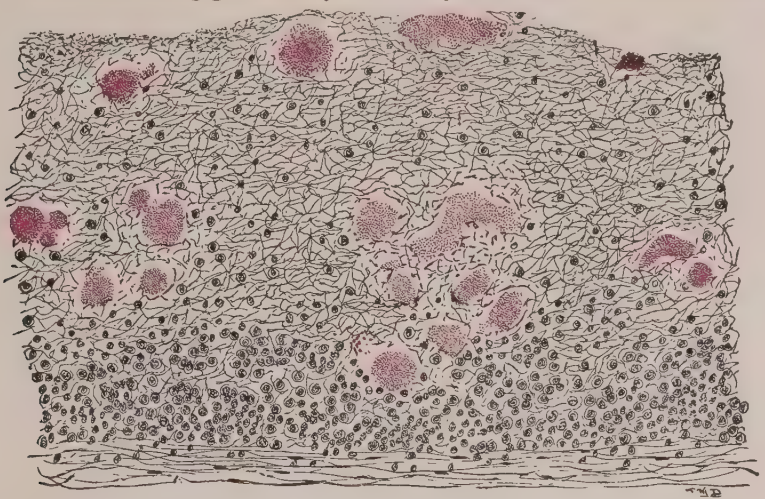


Fig. 124.—Micrococci in Masses in the Fibrinous Exudation of Pyemic Pleurisy.

with any form of demonstrable external lesion. This is often called *cryptogenetic pyemia* or *septicopyemia*.

After death from septicemia and pyemia there is a considerable variety in the post-mortem appearances.

There are cases in which there are no recognizable gross lesions.

There are cases characterized by early post-mortem decompositions; post-mortem staining of the tissues; congestion of the lungs, stomach, intestines, and kidneys; extravasations of blood in the serous membranes; swelling of the solitary and agminated lymph-nodules in the small intestine; swelling of the spleen and albuminous degeneration of the liver and kidneys; chromatolysis of the ganglion cells of the brain and cord.

[1] It has long been known that persons who have received injuries or wounds may suffer from constitutional symptoms, among the most marked of which may be fever, and develop local or disseminated lesions. To designate the condition of these patients the terms *pyemia, septicemia, septicopyemia, pyosepticemia, ichoremia, inflammatory fever, surgical fever, traumatic fever, suppurative fever, puerperal fever*, and *purulent infection* have been used.

There may be localized inflammations. The joints and the tissue about them, the pleura, the pericardium, the endocardium, the peritoneum, the pia mater, and the connective tissue in different parts of the body may be inflamed. These local inflammations are usually purulent, except in the serous membranes, where the principal inflammatory product may be fibrin (Fig. 124). The veins in the neighborhood of the wound may contain softened, purulent thrombi, without infarctions in the viscera, while there may be inflammation of the joints and serous membranes. On the other hand, with the venous thrombosis there may be infarctions and abscesses in the viscera; acute inflammations of the joints and serous membranes may be present or absent. While thrombi are often formed in the veins near the wound, they may be situated in veins at a distance, and sometimes, although infarctions and abscesses be present, no thrombus can be discovered. The veins may be distended by the thrombi or contain only small coagula. The different kinds of thrombi, and the varieties of emboli and infarctions which they produce, are described in the section on Thrombosis (page 35). Leucocytosis usually accompanies pyemia and septicemia as well as the suppurative process with which they are associated. Studies of the blood in various forms of septicemia are numerous and instructive, but we cannot consider them here.[1]

Various lines of research on minute changes in cells which bacterial and other poisons may induce, justify the expectation that more and more we shall be able to associate characteristic groups of symptoms in toxemia and septicemia for which there is now no morphological basis, with well-defined cell alterations. Among the most striking of the toxic cell lesions thus far studied in septicemia and bacterial toxemia are those involving the cytoplasm of the ganglion cells (see Nervous System).

THE PYOGENIC BACTERIA.

While many species of microbes are capable under favorable conditions of inciting suppuration and other forms of exudative inflammation and may, when they or their toxins are disseminated in the body, give rise to toxemia, septicemia, and pyemia, there are two forms which, on account of their early discovery and their relative frequency, are commonly considered as *par excellence* "pyogenic" bacteria. These, which are called *Staphylococcus* and *Streptococcus*, we shall consider first.

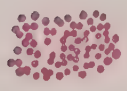


Fig. 125.—Staphylococcus Pyogenes Aureus.
From a bouillon culture.

Characters of Staphylococcus Pyogenes.

The *Staphylococcus pyogenes aureus* (Micrococcus pyogenes aureus) (Fig. 125) is a relatively small coccus, the individuals varying, however, considerably in size (0.4 to 1.2 μ in diameter). In its growth it does not show a characteristic grouping, but grows in irregular masses and heaps (the somewhat crude resemblance, when studied

[1] Consult *White, F. W.*, Jour. Exper. Med., 1899, iv, 425 (bibl.); and *Warren, M.*, and *Herrick, W. W.*, Am. Jour. Med. Sc., 1916, cli, 556.

under a cover-glass, to a bunch of grapes gave rise to the generic name); sometimes, however, pairs and groups of four or short rows of the cocci are seen. The germ is readily stained by the aniline dyes, and does not lose its color in Gram's method of staining. It does not show spontaneous movement, and, like other spheroidal forms, does not appear to develop spores. It is quite tenacious of vitality, surviving long drying and degrees of heat and cold and an exposure to chemical bactericides to which many pathogenic germs readily succumb. It grows well at ordinary room temperature in such artificial culture media as nutrient-gelatin, agar, beef-tea, and milk, and on potato, forming somewhat voluminous masses of culture. It rapidly fluidifies gelatin through the formation of a ferment, it coagulates milk, and in the various media develops a yellowish white or a deep golden yellow color, whence its specific name, *aureus*, and its common name, "golden coccus." Its color-producing capacity is subject to wide variation. Staphylococcus pyogenes aureus forms in old cultures a hemolytic substance [1] which may be demonstrated in plate cultures mixed with red blood-cells (Fig. 126) or in tubes containing the washed corpuscles to which filtrates of old bouillon cultures have been added.

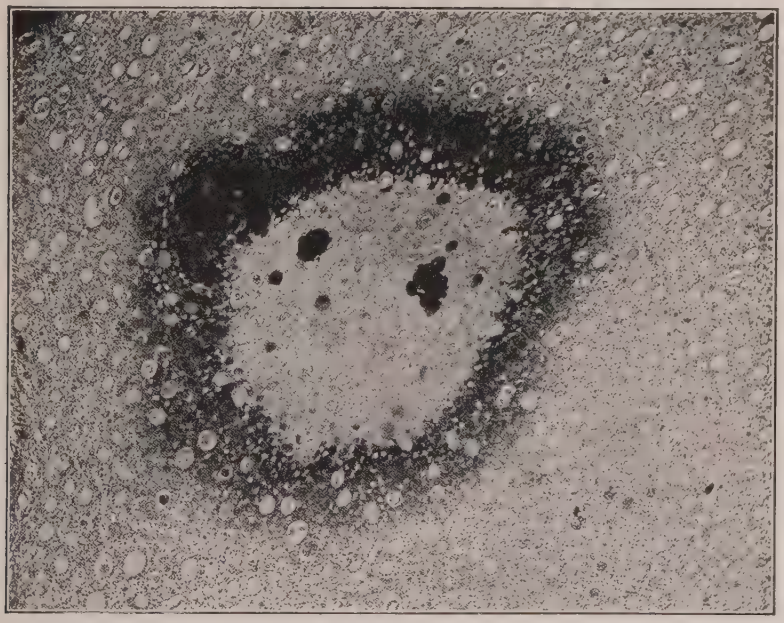


FIG. 126.—INFECTIVE EMBOLUS OF STAPHYLOCOCCUS PYOGENES AUREUS IN THE KIDNEY. RABBIT—EXPERIMENTAL.

Effects of Staphylococcus Pyogenes in the Body.—The virulence of cultures of Staphylococcus pyogenes obtained from different sources varies considerably, but, in general, suppuration is not readily induced in the lower animals by its subcutaneous injection. Liability to suppuration is greatly increased by mechanical or chemical injury to the tissues with which the germ is brought in contact. Injection of a virulent culture into the ear vein of the rabbit is usually followed by multi-

[1] For a study of the bacterial hemolysins see *Pribram*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen. 2d ed., 1913, ii, 1328.

ple abscesses in the kidneys and muscles, by suppuration of joints, etc. (Fig. 126.)

In man this coccus grows readily and rapidly, and may cause necrosis and exudative inflammation, especially the suppurative phases (Fig. 127). The lesions which it induces are apt to be circumscribed, but septicemia and pyemia may result as well as pustules, boils, and abscesses, and various suppurative inflammations of the visceral and serous membranes, joints, bones, endocardium, etc. These effects may be induced by the staphylococcus alone or by it in association with other species of germs. It is frequently associated with Streptococcus pyogenes.

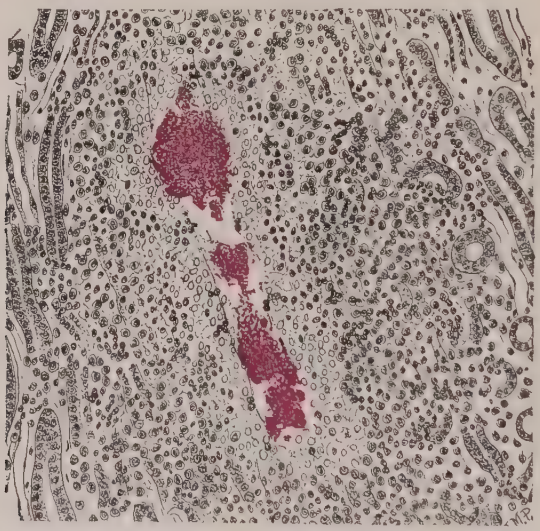


FIG. 127.—MASSES OF MICROCOCCI IN A BLOOD-VESSEL OF THE KIDNEY, INDUCING A SMALL ABSCESS. From a case of pyemia. Around the dilated and partially necrotic blood-vessel in which the bacteria lie is an area of necrotic tissue and a small-cell infiltration or zone of pus.

Staphylococcus pyogenes aureus incites these changes in the body in virtue of certain toxins or toxalbumins which are produced as the result of its metabolism, and which are either at once set free or stored up in the body of the germs—endotoxins—until their release by disintegration after the death of the germs. The special power of the staphylococcus to cause the gathering of leucocytes is apparently due to the marked chemotaxic powers of some of the protein substances in its protoplasm. In its growth in the body staphylococcus may lead to the development of hemolytic, agglutinative, leucocidal, leucolytic, and opsonic substances.

Portals of Entry.—It may enter the body through wounds, small or large, of the skin or mucous membranes, through sweat and sebaceous glands and hair follicles, and sometimes through uninjured surfaces.

In many cases its mode of access is not evident.[1] While usually this germ dies in the body, it may remain for a long time alive.

Sources.—It is widespread in inhabited regions, especially in towns, being frequently found on the surface of the body, and in the saliva, particularly of those with acute or chronic catarrh of the upper air passages. As the result of the filthy habit of indiscriminate public spitting and unguarded sneezing, it is common in the dust of hospitals, houses, towns, public conveyances, and places of public assembly.[2] It is probable, however, that the larger part of the acute staphylococcus infections are incited by organisms derived directly or indirectly from others already infected.

Susceptibility.—In man there may be a susceptibility to Staphylococcus pyogenes associated with a general disease, diabetes for example On the other hand, local susceptibility in man is of frequent occurrence. In chronic furunculosis and in carbuncle, local areas of inflammation may develop and persist for long periods, fresh foci developing as the older ones heal. In some instances this local vulnerability is apparently associated with minor local injuries, such as the friction of garments at the back of the neck, or pressure and friction in the gluteal regions. Sometimes, however, the local vulnerability appears to arise from disturbances in the sebaceous and sweat glands and hair follicles, leading to stagnation of secretions in which the bacteria long persisting on the surface find lodgment and conditions favorable to their development.

The studies of Wright have indicated that in cases of carbuncle and furunculosis the opsonic index[3] for the special strain of staphylococcus concerned may be low, and, further, that by the injection of emulsions of the dead bodies of these organisms—vaccines of Wright—a rapid immunization of the individual, marked by a rise in the opsonic index of his serum may be produced with a speedy decline of the local inflammatory reaction.

Other Forms of Staphylococcus.

Not all the yellow staphylococci found in dust and on the person are pathogenic. These may be indistinguishable from the infective forms by the usual culture methods. They may, however, be differentiated not only by their innocuousness to animals, but in their failure to develop in these either agglutinative or leucolytic substances.

Staphylococcus pyogenes albus.—This appears to be a variety of the Staphylococcus pyogenes which does not develop the yellow color in cultures. It is of frequent occurrence both in connection with the aureus and alone. Its action on the body is similar, but it has seemed to many observers to be in general less virulent.

Staphylococcus epidermidis albus.—This coccus has been described by Welch as of frequent occurrence in the epidermis, and, although of rather feeble pyogenic power, yet seems frequently to cause small stitch-abscesses and moderate suppuration along drainage tubes. It has been regarded as possibly a variety of Staphylococcus pyogenes albus.

Other forms of staphylococcus have been described—S. salivarius pyogenes, S. cereus albus and flavus—but they are apparently of little pathological significance.[4]

[1] For a résumé of the rôle of S. pyogenes aureus in skin disease, with bibl., see *White*, Boston Med and Surg. Jour., 1899, cxli, 235.

[2] For bibliography of S. pyogenes aureus consult article by *Neisser*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 355.

[3] See p. 219.

[4] For a study in differentiation between pathogenic and saprophytic staphylococci see *Geisse* Ztschr. f. Hyg., 1913, lxxvi, 282.

Characters of the Streptococcus Pyogenes

Streptococcus pyogenes is distinguished by the marked tendency of the individuals to hang together in longer or shorter chains (Fig. 128). It is immobile and its staining reactions are like those of *Staphylococcus pyogenes*. The organism grows readily on ordinary culture media, the optimum temperature being 37.5° C., although at 15° to to 20° C. growth still takes place, a useful point in differentiating streptococci and pneumococci. It does not liquefy gelatin. On the surface of agar plates after twenty-four hours at 37° C. the small grayish colonies show, under the microscope, loops and fringes of chain-like cocci along the borders. In broth the organism forms delicate, flocculent masses, which cling to the sides of the tubes, leaving the fluid clear; but occasionally the masses are dense and compact; or growth is diffused throughout the broth, rendering it turbid.

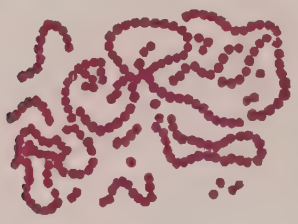


Fig. 128.—Streptococcus Pyogenes.
From a broth culture.

Streptococci are most conveniently divided on the basis of their growth on blood agar plates into two broad groups of *S. hemolyticus* and *S. viridans*. When the colonies are surrounded by a clear hemolyzed zone, the organism is put in the hemolytic group; when they show a definite green color without a well defined zone of hemolysis, it is classed as a viridans. When neither hemolytic zone nor greenish color appears the organism may be considered of indefinite type. Holman[1] has proposed a classification on the basis of carbohydrate fermentation reactions of the two groups of hemolytic and non-hemolytic, comprising eight subgroups. The fermentation reactions have also been used to distinguish the pathogenic and the saprophytic types.[2] Brown[3] has classified the organisms into three groups: Alpha, producing brownish or greenish coloration, but no hemolysis; Beta, producing a zone of marked hemolysis; and Gamma, producing neither hemolysis nor coloration. An Alpha prime type, intermediate between Alpha and Beta, has also been distinguished.

Effects of Streptococcus Pyogenes in the Body.—Streptococci which give evidence of little virulence in animal inoculation are very common in the mouths of healthy persons. The significance of these germs in healthy mouths is not yet clear.

The results of animal inoculation with the Streptococcus pyogenes are in general similar to those with the Staphylococcus pyogenes aureus. The streptococcus is very frequently associated with the staphylococcus in its distribution outside the body, in healthy persons, and in disease. In general it may be said that the streptococcus incites those forms of suppuration and fibrinopurulent inflammation which tend to spread both locally and through metastasis.

Streptococcus pyogenes has been found either alone or in association with staphylococcus in a large number of suppurative and other inflammatory processes in various parts of the body; the condition in some cases receiving special names, in others not. Thus, in boils and carbuncles, in abscesses and phlegmons, in herpes, impetigo, and panaritium,

[1] *Holman, W. L.*, Jour. Med. Research, 1916, xxxiv, 377.
[2] *Hopkins, J. G.*, and *Lang, A.*, Jour. Infect. Dis., 1914, xv, 63.
[3] *Brown, J. H.*, The use of blood agar for the study of streptococci, Monograph No. 9, Rockefeller Institute, New York, 1919.

in phlebitis and lymphangitis, in erysipelas, in suppurative inflammation of various mucous and serous membranes, especially of the throat and the gastrointestinal canal, and of the bones and joints, in some forms of bronchitis and pneumonia, in puerperal and other forms of septicemia, in the pustules of smallpox, one or other or both of these germs are frequently concerned.[1]

One of the most important features of the relationship of Streptococcus pyogenes to man is the frequency with which it enters as a concur-

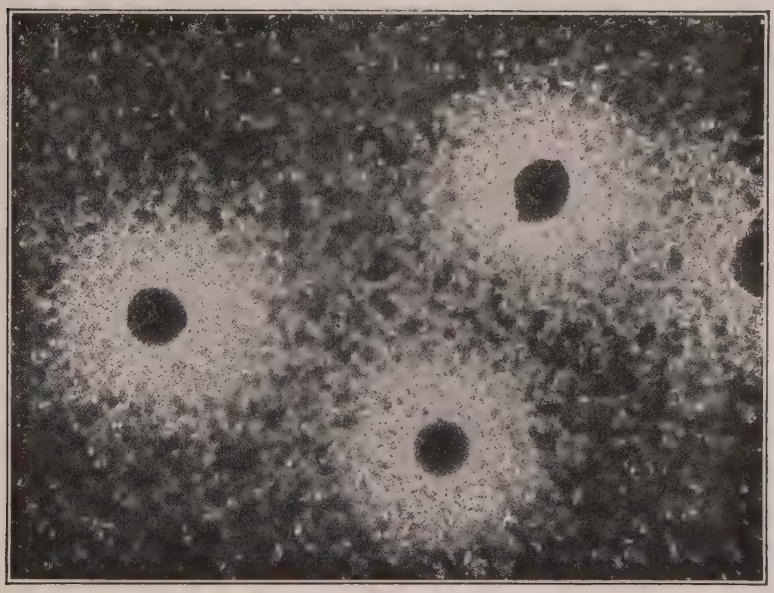


FIG. 129.—HEMOLYSIS BY STREPTOCOCCUS.

The streptococcus was grown in a culture medium with which red blood-cells were mixed. Around each colony the color has left the red blood-cells and is diffused through the plate.

rent pathogenic agent in already established infectious diseases due to other forms of microorganisms. Thus, some of the most serious complications to which the victims of scarlatina, diphtheria, typhoid fever, and pulmonary tuberculosis are liable are due to the action of the streptococcus in a body rendered unusually vulnerable by the existence of another form of infection.

The serum of individuals adapted (immunized) to streptococci may agglutinate the homologous microorganisms.[2]

Streptococci, which upon their isolation from the body in suppurative or other infectious processes are very virulent, usually, and sometimes

[1] Anaerobic streptococci have been found by various observers in abscesses and other forms of suppuration of which they are apparently the excitants.

[2] For a study of agglutination of streptococci see *Moser* and *v. Pirquet*, Centralbl. f. Bakteriol., Orig. I., 1903, xxxiv, 560 and 714: also *Neufeld*, Ztschr. f. Hyg., 1903, xliv, 161: also *Weaver*, Jour. Infect. Dis., 1904. i, 91.

very quickly, partially or wholly lose this virulence under artificial cultivation. On the other hand, cultures of streptococci which have largely lost virulence under artificial cultivation, or whose initial virulence was slight, may experience a great exaltation of virulence by a long succession of inoculations from animal to animal.[1]

In streptococcus infections hemolytic, agglutinating, and opsonic substances may be formed in the body.

Artificial Immunity.—The metabolic products formed by virulent streptococci growing in nutrient broth have been found to induce in animals the symptoms of toxemia. The results of preliminary experiments on immunization with these toxic products, and the dead and living bodies of the germs and the use of the blood-serum of the immune animal for therapeutic purposes, are complex, and along the present lines of work apparently not very promising.

SEPTIC SORE THROAT.

There have been known for some time in England, and recently have occurred in several localities in the United States, serious epidemics of inflammation of the throat and tonsils associated with particular milk supplies. The milk apparently is contaminated by a streptococcus from the inflamed udder of cows or from the throats of the milk handlers. This organism closely resembles Streptococcus pyogenes and has been called Streptococcus epidemicus.[2]

ERYSIPELAS.

Erysipelas is a diffuse inflammation of the skin and subcutaneous tissue which tends to spread, and is characterized locally by swelling of the tissue and a bright red color of the integument. It is usually accompanied by constitutional disturbances, the most marked of which is fever. The morphological changes at the seat of lesion, as we see them after death, vary considerably in different cases and in different stages of the disease. The redness of the skin usually disappears after death. But the tissues may be swollen by the accumulation of serous fluid. This fluid may be nearly transparent, or turbid from admixture with pus cells (Fig. 130). Pus cells may infiltrate the tissues either sparsely or in dense masses. Fibrin may be present, abscesses may form. Sometimes vesicles or scabs are found on the surface, or the affected region may become gangrenous. Aside from the local lesions, there may be toxemia marked by petechiæ in the serous membranes, swelling of the spleen, focal necroses, and albuminous degeneration in the kidneys and liver.

[1] For bibliography of streptococcus consult the article by *v. Lingelsheim*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 453; for a study of the action of the toxin on various parts of the body, see *Homén* and others, Zieglers Beitr., 1899, xxv, 1ff.

[2] For a summary of such epidemics and a study of the streptococcus, see *North, C. E.*, Jour. Infect. Dis., 1914, xiv, 124.

The most common excitant of erysipelas is Streptococcus pyogenes.[1] This organism may be present in large numbers in the lymph-vessels, especially in the borders of the inflamed region. The reasons for the clinical peculiarities of this phase of inflammation are not yet very clear.

INFECTIOUS PSEUDOMEMBRANOUS INFLAMMATION OF MUCOUS MEMBRANES. (Pseudodiphtheria; Diphtheroid Angina; Membranous Angina.)

Under a variety of conditions, as during scarlatina and measles, whooping-cough, typhoid fever, etc., or entirely apart from any complicating disorder, an acute exudative inflammation of the mucous mem-

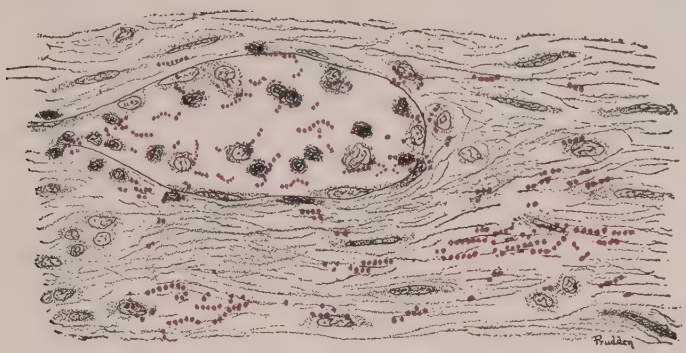


FIG. 130.—ERYSIPELAS OF THE SKIN.
Showing streptococci in the lymph-spaces.

branes, especially of the upper air passages, occurs, which is associated with and is apparently induced by the growth of Streptococcus pyogenes.[2] There may be much or little fibrinous exudate; there may in early stages, or even throughout, be none at all. The pellicle when formed may be loose or adherent, sharply circumscribed or tending to spread. The submucous tissue may show little change, or may be congested and edematous, or may be the seat of suppurative inflammation (see Fig. 131), necrosis, or gangrene. The process may be confined to the tonsils. While under these varying conditions the inflammatory process is usually a local one and runs its course with or without the symptoms of septicemia, occasionally the streptococcus which enters the blood may induce the lesions of pyemia. On the other hand, it may by aspiration gain access to the lungs and induce varying phases of complicating bronchopneumonia. The Staphylococcus pyogenes is not infrequently associated with the streptococcus in these lesions, but is not apparently of primary significance.

Simulating very closely, as it does in many cases, both the local and

[1] In the early days of modern bacteriology the "chain" coccus which was discovered in the exudate of erysipelas was thought to bear a peculiar relationship to this clinical form of phlegmonous inflammation and was called by *Fehleisen* Streptococcus erysipelatis, but it has now been definitely identified with the S. pyogenes.

[2] *Prudden*, Med. Rec., 1891, xxxix, 445; *Baginsky* and *Sommerfeld*, Berl. klin. Wchnschr., 1900, xxxvii, 588, 618.

general phenomena of diphtheria, this disorder has formerly been confounded with it, and has only recently been recognized as a distinct phase of disease. It is now most frequently called pseudodiphtheria. It seems in part to cover the condition formerly known as croup, in part those cases formerly thought to be mild diphtheria. In many phases of acute angina, and in many cases of follicular tonsillitis, streptococci

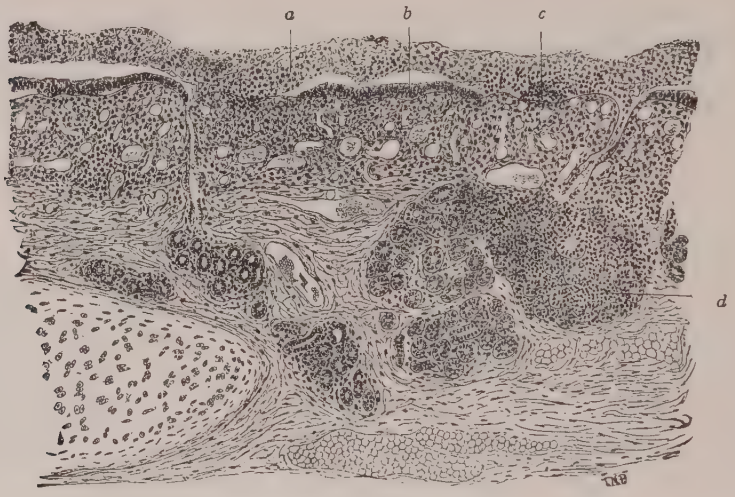


FIG. 131.—PSEUDOMEMBRANOUS INFLAMMATION OF TRACHEA.

In this case there is purulent infiltration of the mucosa and submucosa, and of portions of the mucous glands. *a*, False membrane; *b*, portion of intact epithelium; *c*, infiltration of the mucosa with fibrin; *d*, portion of mucous gland infiltrated with pus.

have been found in large numbers. Other bacteria, either alone or in association with the pyogenic cocci, may be excitants of pseudomembranous as well as simple angina.

OTHER BACTERIA WHICH ARE FREQUENT EXCITANTS OF SUPPURATION.

While the Staphylococcus pyogenes and Streptococcus pyogenes are the most common excitants of local suppuration with and without toxemia and septicemia, such conditions, as we have seen, are not infrequently due to other microorganisms. Among these we may mention here as the more common and important:—Diplococcus pneumoniæ, the gonococcus, Micrococcus tetragenus, Bacillus pyocyaneus, the colon and the typhoid bacillus, the bacillus of glanders, the tubercle bacillus, the pneumobacillus of Friedländer, the diplococcus of cerebrospinal meningitis, Bacillus pyogenes fœtidus, and actinomyces with its related forms.

In some of these organisms the pyogenic qualities in their relationships to human infections are most conspicuous; in others, the reaction of the body to their presence is such as to justify a special name. The

latter is particularly noteworthy in the case of the pneumococcus, the gonococcus, glanders, typhoid, and tubercle bacilli, Diplococcus meningitidis, and actinomyces.

Many other microorganisms may be excitants of suppurative inflammation in man as well as in the lower animals under experimental conditions, but this exceptional reaction of living tissues does not fall within the scope of this work, which deals primarily with such tissue reactions as may occur under the usual conditions of life.

The Bacillus Coli Communis and the Colon Group.

The *Bacillus coli communis* is an organism so commonly present in the intestines under normal conditions as usually to be called the "colon bacillus." It is motile, facultative aerobic, asporogenous, considerably resembling in general form the typhoid bacillus (see page 271). It grows readily in artificial cultures and does not fluidify gelatin. It has been repeatedly found in connection with suppurative processes under such conditions as to justify the belief that it is often their excitant.

It has been found in various forms of peritoneal suppuration, both with and without such lesions of the intestine as would obviously permit of its egress; in appendicitis; in suppuration about the gall-ducts; in hemorrhagic pancreatitis; and in inflammatory processes in the genito-urinary apparatus; frequently in the bladder, in the pericardium and pleura; and it is believed to be concerned in certain types of diarrhea. It is often demonstrable in terminal infections.

Local infection with this organism is often associated with serious toxemia and septicemia. Intravascular injections of virulent cultures in rabbits are usually followed by symptoms and lesions of septicemia. Introduced subcutaneously and intraperitoneally, it may excite local suppuration or serofibrinous inflammation, often hemorrhagic in character, terminating fatally.[1]

It is not possible to indicate very definitely all the conditions under which the colon bacillus, an ordinarily harmless intestinal saprophyte, may gain access to the tissues and become actively pathogenic. Whether it is special strains of the bacillus coming in from without which are pathogenic, or whether the ordinary forms assume virulent capacities under unknown conditions, we cannot tell to-day. It appears in any event that very slight damage to the mucous membrane of the intestinal tract which may permit the exit of the germs, or the existence of damaged tissues elsewhere in the body—in the kidney, ureter, peritoneum, etc., for example—favor infection with this organism. To what extent a reduction in efficiency of the protective fluids of the body may determine infection we cannot say with certainty. Shortly after death the colon bacillus may pass from the intestine into the tissues, and the possibility of this post-mortem invasion should be borne in mind

[1] For details concerning B. coli, see *Conradi* and *Bierast*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, vi, 483.

in the examination of cultures from the dead body, since it may readily and doubtless often does give rise to errors in diagnosis.

The Colon Group.—There are so many organisms so closely resembling the colon bacillus in their morphological and biological characters that it has been found convenient to consider them as possible variations of one form and to speak of them collectively as the "colon group." The differentiation between the individual members of this group and between these and the typhoid bacillus has presented many difficulties to bacteriologists and given rise to much technical finesse.[1]

The Bacillus Pyocyaneus.

The occurrence of brilliant greenish or bluish pus in superficial wounds has been noted for over a century, although the organism causing it was unknown until its isolation by Gessard in 1882. The organism was not regarded as possessing any special pathogenic qualities until 1898 when Charrin published a study of the disease induced by its growth, under the name "la maladie pyocyanique." His observations were confirmed by Schimmelbusch, and since that time the Bacillus pyocyaneus has been recognized as a widespread organism occurring in air, dust, water, and the intestinal contents of man and animals, and regularly infesting the skin of the human body, especially the axillary and inguinal folds. It is also found saprophytically in the external auditory meatus. Its occurrence has been noted in purulent otitis media, in acute throat infections, in endocarditis and pericarditis, in inflammations of the urinary tract, in meningitis, in bronchopneumonia, and in gastrointestinal disturbances in infants and adults. A moderate number of cases of general infection with isolation of the organism from the circulating blood have been reported.[2] It is frequently found in the blood post-mortem, but its presence is then considered to be due to a terminal invasion from the intestinal tract and not to a true infection. The infection by the organism of superficial wounds, especially abdominal incisions for the drainage of appendical abscesses, is frequent; as a rule, however, it merely delays the healing process and does not seem to play a more active part. In closed cavities, on the contrary, it is highly pathogenic. Among the more marked lesions which are usually present in cases of pyocyaneus infection are albuminous degeneration of the viscera, focal necroses, hyperplasia of the lymph-nodes, hemorrhages, and especially superficial, circumscribed or diffuse necrosis and ulceration in the intestinal mucous membrane. The most striking characteristic is the hemorrhagic nature of the lesions.

Characters of the Organism.

The Bacillus pyocyaneus is a slender rod, is motile, and is negative to Gram. It grows readily on artificial media, liquefies gelatin, and ultimately forms pigment. It is highly pathogenic for rabbits and guinea-pigs.[3]

[1] See *Hiss*, Jour. Exper. Med., 1897, ii, 677; Jour. Med. Research, 1902, N. S. iii, 148; *Hiss* and *Russell*, Med. News, 1903, lxxxii, 289.

[2] *Brill* and *Libman*, Am. Jour. Med. Sc., 1899, cxviii, 153 (bibl.).

[3] For further details see *Voss*, Der Bacillus pyocyaneus im Ohr, Berlin, 1906; and *Heller* and *Lepère* Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 1185.

Bacillus Mucosus Capsulatus (*Friedländer Bacillus*).

In a small proportion of cases of lobar and lobular pneumonia, and in a few cases of exudative inflammation of the pleura, pericardium, meninges, nose, throat, and middle ear, this short encapsulated bacillus has been found. It is sometimes found alone, but in pneumonia is often associated either with the pneumococcus or with the pyogenic cocci. It has been found in the nasal secretion and mouths of healthy persons and in the intestinal contents. While belonging definitely among the bacilli, it so frequently occurs in the form of very short rods or ovals or short chains that it was formerly thought to belong among the cocci. It is readily cultivated on artificial media and is slightly pathogenic for certain animals.

This germ was formerly believed to be of great importance in connection with acute lobar pneumonia, and for a time was generally spoken of as the pneumococcus of Friedländer. It is now known not to be a coccus, and is certainly of subordinate, though occasionally serious, importance in inducing inflammation of the lungs.[1] In a few instances its presence in the spinal fluid and the blood has been proved.

Micrococcus Tetragenus.

This organism has been many times found about the mouth and respiratory tract, especially in connection with suppurative processes, tuberculous cavities, etc. It has been found also in metastatic abscesses. While not very virulent it is apparently an occasional excitant, either alone or with other organisms, of suppuration.

Characters of the Organism.

It is a coccus about 1 μ in diameter, usually occurring in groups of four. These tetrad groups may be encapsulated. It stains by Gram's method, and is readily cultivated on artificial media. It forms a dense whitish growth on gelatin, which it does not fluidify. Septicemic lesions with local suppuration may be induced in guinea-pigs by subcutaneous injection with cultures.

The Proteus Group of Bacilli.

This is a large and, in the economy of nature, an important group of bacilli much concerned with the putrefactive processes.

Characters of the Group.

The bacilli of this group may be aerobes or facultative anaerobes. They are of medium size, asporogenous, and while staining readily with ordinary dyes are apt to be decolorized by the Gram method. While the organisms of this group are bacilli, they often present considerable variation in form as they grow, sometimes being very

[1] *Howard*, Philadelphia Med. Jour., 1898, i, 336; and Bull. Johns Hopkins Hosp., 1899, x, 66; *Stuhlern*, Centralbl. f. Bakteriol., Orig. I., 1904, xxxvi, 493; *Perkins*, Jour. Infect. Dis., 1904, i, 241.

short so as to resemble cocci, sometimes forming threads which may be so bent as to suggest spirals. Their growth on solid media is especially characterized by the tendency to send runners from the central growth out into the surrounding media, thus establishing secondary growth centers. They are particularly sensitive to environment, so that physiological as well as morphological variations are frequent. It is for these reasons that the name Proteus has been given to the group and to various species. The limitations of the named species are, however, in many cases quite ill defined.

One of the most common forms has been called *Proteus vulgaris*. While this bacillus is very widespread, it is only occasionally the excitant of pathological processes in man, and then almost always in concurrence with other organisms, usually the pyogenic cocci. Under these conditions a suppurative inflammation with foul exudate is apt to develop. Thus it has been found in purulent peritonitis and endometritis, in pleurisy and in phlegmonous inflammation in various parts of the body. Although this bacillus is not apt to grow in the human body, except in association with other microorganisms which may damage the tissues or in tissues already vulnerable from injury, it may in the bladder independently incite an exudative inflammation. In animals, subcutaneous injection of the pure culture in considerable quantity may lead to abscess, while the soluble products of broth culture may induce toxemia.

Several other forms of Proteus, as well as closely related species, have been found in human lesions for the most part suppurative and necrotic in character, and these, in some cases, have been conclusively shown to be the excitants of the pathological processes, but the scope of this work does not permit further details.

OTHER PYOGENIC BACTERIA.

Among the other bacteria which commonly induce local suppuration, with or without toxemia and septicemia, some are of frequent occurrence as excitants of such well-marked and more or less characteristic forms of disease as have long been recognized clinically and have received special names, such as pneumonia, gonorrhea, cerebrospinal meningitis, etc. The tubercle bacillus may also induce suppurative inflammation. These will be in part considered in the section dealing with the organs in which their more characteristic lesions are manifested.

ACUTE LOBAR PNEUMONIA AND OTHER INFECTIOUS DISEASES INDUCED BY THE DIPLOCOCCUS PNEUMONIÆ (Pneumococcus Lanceolatus).

Diplococcus pneumoniæ is sometimes spoken of as the "pneumococcus of Fränkel," because its significance and life history in connection with acute lobar pneumonia were first demonstrated by him.[1] It is commonly called simply the "pneumococcus."

[1] It was discovered by Sternberg in saliva, and its pathogenic power demonstrated some years before its full significance in connection with pneumonia was understood.

Characters of the Diplococcus Pneumoniæ.

During active growth these germs are spheroidal; but in their mature condition they are apt to become slightly elongated or oval and are often a little broader at one end than at the other, assuming a lanceolate form. They are very apt to occur in pairs, and frequently are seen in short chains, rarely in long. Very frequently in the living animal, the pneumococcus is surrounded by a distinct, homogeneous capsule of varying thickness (see Fig. 132). Except in certain media capsule development is not well marked. The coccus itself is readily stained by the aniline dyes and retains the stain by Gram's method; the capsule is not easily demonstrated except by special staining methods.[1]

The pneumococcus has no spontaneous movement. No growth is obtainable at 20° C., but at 37° C. there is a fairly abundant yield, forming on the surface of blood-serum or on very slightly alkaline glycerin-agar plates faint grayish, dewdrop like, inconspicuous colonies, somewhat similar to those of Streptococcus pyogenes, but usually more delicate. As a rule, the cultures soon lose their virulence and die off, but the virulence may be maintained by successive inoculations in suitable animals. The pneumococcus may remain viable and virulent for many days when dried in sputum but in the form of small particles such as are distributed in coughing and sneezing it remains alive, for from one to one and a half hours.[2] In direct sunlight it may die in a few moments.

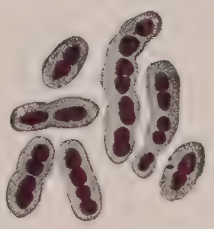


Fig. 132. Diplococcus Pneumoniæ Pneumococcus.
Showing the stained capsules.

The serum of persons suffering from acute lobar pneumonia, as well as the serum of lower animals artificially immunized to the Diplococcus pneumoniæ, induces agglutination of the organism in broth cultures. By the use of centrifugated cultures of the organism, the reaction of agglutination can be obtained in much greater dilution than by the usual method.[3] Precipitins are found in immune sera.

Cultures which have been reduced in virulence, so as not to cause early death by septicemia, may, when introduced into the trachea of rabbits, induce circumscribed pneumonic lesions, especially if these animals are made vulnerable by cold or by other agencies which impair the integrity of the blood or other tissues. By partially immunizing rabbits to the pneumococcus, so that they do not speedily die from septicemia, and then introducing the virulent organism into the lungs through the trachea, diffuse pneumonic lesions comparable to the lobar pneumonias of man may be induced.[4] Lesions of lobar pneumonia are readily induced in the dog by intratracheal injections of the pneumococcus.[5] Blake and Cecil have succeeded in producing in monkeys various types of pneumonia which are quite analogous to the forms occurring in man.[6] Whether under natural conditions of infection the pneumococcus is always directly introduced into the smaller bronchi or alveoli of the lung by inhalation, as has been generally assumed, is still not definitely decided. The idea has been brought forward that another route may be of great importance, that is, the lymphatics in the submucosa of the trachea and bronchi.[7] But the current belief is that in the majority of instances the organisms are introduced by inhalation.

This germ is the incitant of typical lobar pneumonia in man and in a large proportion, if not in all, cases is present in the blood at some time in the course of the disease, though in the earlier stages it can be demonstrated in only about 30 per cent.[8] In the severer types of the disease, pneumococci appear in the spinal fluid, even though no complicating

[1] See *Wadsworth, A.*, Jour. Infect. Dis., 1906, iii, 610.
[2] *Wood, F. C.*, Jour. Exper. Med., 1905, vii, 592.
[3] For details of this method see *Wadsworth, A.*, Jour. Med. Research, 1903; N. S. v, 228.
[4] See *Wadsworth, A.*, Jour. Exper. Med., 1912, xvi, 54, 78 (bibl.).
[5] *Lamar* and *Meltzer*, Jour. Exper. Med., 1912, xv, 133; and *Wollstein* and *Meltzer*, ibid., 1912, xvi, 127.
[6] *Blake, F. G.*, and *Cecil, R.*, Jour. Exper. Med., 1920, xxxi, 403, 445, 499; 1920, xxxii, 401, 691.
[7] *Winternitz, M. C., Smith, G. H.*, and *Robinson, E. S.*, Bull. Johns Hopkins Hosp., 1920, xxxi, 63.
[8] See *Rosenow*, Jour. Infect. Dis., 1904, i, 280; also *Dochez, A. R.*, Jour. Exper. Med., 1912, xvi, 680.

meningitis may occur.[1] It induces locally in the lungs an acute exudative inflammation associated with an enormous multiplication of the germ and a toxemia due to the distribution of soluble toxic products through the blood.

For a more detailed description of the lesions of pneumonia and an account of other bacteria which may be present, see page 695.

Recent studies of the pneumococcus have added much to our knowledge of its biological characters. Neufeld and Händel[2] first showed that this group contained a variety of organisms, and their observations, so far as the occurrence of groups in the United States is concerned, have been confirmed by other investigators by means of precipitin and agglutination reactions and by tests on mice.[3] The organism may be divided into two main groups, the larger of which contains Types I, II, and III, comprising from 75 to 80 per cent. of all strains encountered in lobar pneumonia, while the smaller contains Type IV, a broad group of less virulent organisms all true pneumococci which can not be serologically identified with the other three types. Type I is the form which is most often the cause of pneumonia in man, and is found in about one-third of all cases of lobar pneumonia. Type II is nearly as frequent; Type III is responsible for about 15 per cent. of cases, and Type IV for the remainder. Type III corresponds to an organism formerly designated *Streptococcus mucosus capsulatus*, but now included among the pneumococci because of its solubility in bile, its capacity to ferment inulin, and its pathogenic properties.

In addition to these four types, there are many subgroups, chiefly of Type II. Lister, working in South Africa, distinguished a strain which he called Type A; but this has not yet been identified in the United States.[4] It seems probable that in addition to these type variations in different parts of the world, there are also great fluctuations in virulence and possibly also in precipitin and agglutination reactions of the organisms found in the same locality, so that slight differences in groupings will probably occur from year to year. For example, in the 1917–19 epidemic in the United States war hospitals, Type IV was found to be the infecting organism more often than all the other types combined, and similar accidental fluctuations will no doubt be observed in different populations and under different conditions.

The rapid identification of the organisms, which is important for therapeutic reasons since a serum seems to be of value in the treatment of infections with Type I, may be made by the examination of smears or by precipitin or agglutination tests. For technical methods of differentiation the standard textbooks should be consulted.[5]

[1] *Rohdenburg, G. L.*, and *Vander Veer, A.*, Jour. Am. Med. Assn., 1915, lxiv, 1227.

[2] *Neufeld* and *Händel*, Arb. a. d. k. Gsndhtsamte, 1910, xxxiv, 293.

[3] *Dochez, A. R.*, and *Gillespie, L. J.*, Jour. Amer. Med. Assn., 1913, lxi, 727; *Avery, O. T.*, Jour. Exper. Med., 1915, xxii, 804; *Avery, O. T.*, *Chickering, H. T.*, *Cole, R.*, and *Dochez, A. R.*, Acute lobar pneumonia: Prevention and Serum Treatment, Monograph No. 7, Rockefeller Institute, New York, 1917.

[4] *Lister, F. S.*, Publications of the South African Institute for Medical Research, 1913, No. 2; 1916, No. 8; 1917, No. 10.

[5] *Hiss* and *Zinsser*, Textbook of Bacteriology, 5th edition, New York, 1922; *Wood, Vogel*, and *Famulener*, Laboratory Technique, 2d edition, New York, 1922.

In addition to its more common effect in inducing lobar pneumonia, the pneumococcus is frequently the excitant of exudative inflammation in other parts of the body, either with or without a primary lobar pneumonia. Thus it has been repeatedly found in pleuritis, otitis, meningitis, empyema, pericarditis, endocarditis, and peritonitis. It has been found in abscesses of the viscera and in exudative inflammation of the joints. It may induce pseudomembranous inflammation of the mucous membranes, and is a frequent cause of corneal ulcer. Leucocytosis usually accompanies infection with the pneumococcus.

Sources of Pneumococcus.—The pneumococcus has been found in the mouths of a large proportion of healthy persons. In more than half such instances the organism belongs to Type IV which is apparently usually less virulent than the other strains. Type III is the organism present in about one-third of the cases, and Type II-*x*, a special subdivision, in about one tenth.[1] The organism is thrown off in the sputum in lobar pneumonia, and no doubt from this source, to a certain extent in the dried condition, as dust, but more often in the droplets of sputum ejected in the coughing of pneumonics or in the fine spray formed in sneezing,[2] furnishes the infectious agent which in favoring conditions of the body lights up the inflammatory process in the lungs.[3] Convalescents or persons who have been in contact with pneumonic patients may act as carriers[4] of Types I and II. The occurrence of house epidemics due to one or the other of the types described has demonstrated that pneumonia must to a certain extent be regarded as a communicable disease.

Toxic Products of the Pneumococcus.—Although clinically pneumonia bears many marks of toxemia, investigators have not thus far succeeded in finding evidence that, either in artificial cultures or in the infected body, very potent soluble toxins are given off through the metabolic activities of the pneumococcus. There is evidence, on the other hand, that the toxic effects may be induced by endotoxins which are set free when in the course of the disease the organisms die and suffer lysis.[5]

The Crisis in Pneumonia.—The dramatic character of the crisis in many cases of pneumonia has led to much conjecture as to the changes in the body fluids or the bacteria which may occur at this time. There appears to be no marked development of bactericidal power of the serum alone; antitoxic substances are not demonstrable. It has been conjectured that the study of the opsonins might throw light upon the rôle

[1] For a consideration of the pneumococcus of the mouth in healthy persons, and for a study of varieties or strains of pneumococci, see studies carried on under the auspices of the Medical Commission for the Investigation of Acute Respiratory Diseases of the Department of Health of the City of New York, by *Park* and *Williams: Collins: Longcope* and *Fox: Norris* and *Pappenheimer: Duval* and *Lewis: Buerger: Hiss:* and *Longcope:* Jour. Exper. Med., 1905, vii, 401, 626; also *Eyre* and *Leathem*, Jour. Path. and Bacteriol., 1906, xi, 246.

[2] See *Wood, F. C.*, Jour. Exper. Med., 1905, vii, 592.

[3] For study of communicability, see *Edsall* and *Ghriskey*, Tr. College of Phys., Philadelphia, 1904, xxvi, 6. For a study of disinfection of the mouth and of sputum, see *Wadsworth*, Jour. Infect. Dis., 1906, iii, 610.

[4] See *Kolmer* and *Steinfield*, Jour. Am. Med. Assn., 1918, lxx, 14, on disinfection of pneumococcus carriers; also Jour. Infect. Dis., 1918, xxii, 220.

[5] See *Cole, R.*, Jour. Exper. Med., 1912, xvi, 644.

of phagocytes. But in spite of much research no very decisive data have as yet been elicited.

While the crisis in pneumonia is a striking feature in its symptomatology it is only an accentuation of phenomena which occur in recovery from all infections. In pneumonia, as in other infections, two phases of the bacterial action are to be recognized: first, the capacity to proliferate in the host, and, second, the potency of the toxic substances elaborated and set free in the body during the disease. Thus far in most of the experimental and critical studies of pneumonia the reactions of the cells of the host resulting in the production of protective substances have received chief attention. Many believe with Neufeld that bacteriotropic or opsonic substances play an important rôle. Others, as Römer, think that the chief factors in recovery from pneumonic infection are bactericidal substances of unknown nature in the serum. But it is not definitely known at present what the substances are upon which recovery depends.[1] Although both of these agencies may be important, the capacity for growth of the pneumococcus in the body, and the mechanism for the neutralization of the poisons developed in infection are also important, and the consideration of both classes of factors is necessary in an adequate survey of pneumonia.

For in this as in every other infection, the reaction of the microorganism as well as that of the host is decisive in the destruction of the invasive germs, as in the neutralization of the poisons, whether these are derived from the bodies of the bacteria, or in ways apparently more subtle because less clearly understood.[2]

While it has been assumed that the crisis in pneumonia is associated with the beginning of active autolysis, it has only recently been shown that the latter probably depends on an alteration in the ferment-antiferment balance of the blood. In this connection it has been demonstrated that the crisis is usually accompanied by a decrease in the serum antiferment with a concomitant mobilization of specific proteases in the serum and an increase in the serum lipase. The fibrin and leucocytic débris of the exudate must be regarded as one of the potential sources of the toxic substance giving rise to the clinical phenomena of the disease. The rapid autolysis which sets in at the crisis is accompanied by a decrease in the non-coagulable nitrogen and of the proteoses in the blood-serum, which is synchronous with a great increase in the nitrogen excretion in the urine.[3]

Staining Reactions.—For staining the pneumococcus with its capsule the following method of Hiss[4] gives good results. Mix the exudate or culture containing the organism on the cover-glass with a drop of blood-serum spread thin, dry and fix by heat. Add a few drops of the following stain: 5 or 10 per cent. solution of gentian violet (5 c.c. saturated alcoholic solution of gentian violet plus 95 c.c. distilled water).

[1] See *Cole, R.*, Harvey Lecture, Arch. Int. Med., 1914, xiv, 56; also *Hektoen, L.*, Jour. Am. Med. Assn., 1914, lxii, 254 (bibl.); and *Dochez, A. R.*, Jour. Exper. Med., 1912, xvi, 665.

[2] For studies on pneumococcus infection and the mechanism of recovery, see *Wadsworth, A.*, Jour. Exper. Med., 1912, xvi, 54, 78 (bibl.).

[3] *Jobling, Petersen,* and *Eggstein,* Jour. Exper. Med., 1915, xxii, 568.

[4] See, on methods of staining encapsulated pneumococci, *Hiss, P. H.*, Jour. Exper. Med., 1901–5, vi, 317; also *Wadsworth, A.*, Jour. Infect. Dis., 1906, iii, 610.

Heat gently until steam rises. Wash off the stain with a 20 per cent. solution of cupric sulphate. Dry and mount in balsam.

If the material containing the organisms already contain serum, the preliminary mixing with this is unnecessary. Pneumococci in sputum, which without the addition of serum are often stained, with it not infrequently give better results.

The method of Welch[1] gives good results, but annoying precipitates often form. After drying and fixing the specimen upon the cover-glass in the usual way, it is treated with glacial acetic acid, which is at once drained off and replaced by aniline-gentian-violet solution, this being drained off and renewed several times until the acetic acid is displaced. The specimen is now washed with a 2 per cent. solution of sodium chloride, in which it may be covered and studied. The pneumococcus may be stained in sections by Weigert's modification of Gram's method with preliminary contrast stain. By this method the fibrin in pneumonic exudate is also stained.[2]

GONORRHEA AND OTHER INFLAMMATORY LESIONS INDUCED BY THE MICROCOCCUS GONORRHŒÆ (Gonococcus).

The *Micrococcus gonorrhœæ* (gonococcus) is most commonly found in the exudate of gonorrheal inflammation of the mucous membranes, especially of the urethra. It may be free or inclosed in leucocytes or other cells (Fig. 133), or within or between the epithelial cells. The organism may be distributed from the seat of primary lesion, giving rise to gonorrheal arthritis, to malignant endocarditis, to exudative inflammation of the pleura, and to inflammatory processes in other parts of the body.[3]

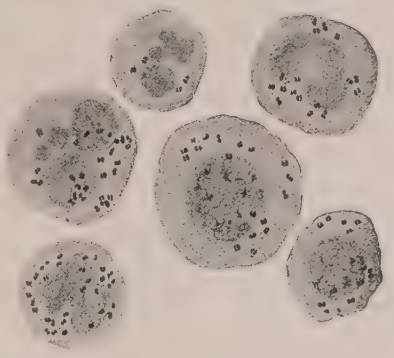


Fig. 133.—Micrococcus Gonorrhœæ in Cells.—Specimen from the Urethra.

The gonococcus may in the primary as well as in the secondary lesions be associated with the pyogenic cocci, the colon bacilli, or other microorganisms. These associations have been observed in cases of pyemia following gonococcal infection. The gonococcus is usually most abundant in the urethra during the acute stage of the inflammation. But long after the organisms have disappeared from the urethral discharge they may be present in small numbers in the deeper portions of the urethra or in the prostatic secretions whence, under favoring conditions, a fresh infection may arise. In the female the inflammation develops in the urethra and cervix, and, through the transportation of the gonococci, may extend along the mucous membrane to the uterus and into the Fallopian tubes. The germs may enter the peritoneum, inducing exudative inflammation. Hyperplasia and suppuration of lymph-nodes near the inflammatory region may

[1] *Welch*, Bull. Johns Hopkins Hosp., 1892, iii, 128.

[2] For a full résumé of studies on the pneumococcus, see *Neufeld* and *Händel*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 513.

[3] Consult, for cases and bibliography, *Young*, Welch Anniversary Contributions to the Science of Medicine, 1900, p. 677; also, *Elting*, Albany Med. Ann., 1900, xxi, 144 (bibl.).

occur. Gonorrheal conjunctivitis is similar in origin and character to the inflammation of the urethra. In the gonorrheal vaginitis of children the organism, although highly transmissible, is frequently of such low virulence that conjunctival inoculation does not result in a blenorrhea.

Characters of the Gonococcus.

The gonococcus is apt to occur in pairs, the apposed sides being more or less distinctly flattened (Fig. 134). It stains readily with the aniline dyes, and differs from most known cocci which might be mistaken for it in that it is decolorized by the iodine solution in the Gram method of staining. It is well after the decolorization by this method, and before mounting in balsam, to make a contrast stain with a dilute aqueous solution of Bismarck brown. Then the gonococci will be of light-brown color, while most other germs of similar morphology will retain the violet color.

Fig. 134.—Micrococcus Gonorrhœæ (Gonococcus). From culture.

The gonococcus is non-motile and does not grow at ordinary room temperatures nor on the ordinary solid or fluid culture media. It may, however, be cultivated at the temperature of the body on human blood-serum, on a combination of this with agar, or on starch agar.[1]

In serum-agar the surface growth of the gonococcus is in the form of small circular, sharp-edged, slightly raised, nearly transparent colonies, coarsely mottled in the central portion, finely granular toward the borders. The life of the colonies under artificial culture is short, but by frequent transference to fresh media it may be maintained indefinitely and gradually adapts itself to the artificial environment.

The gonococcus is readily killed by heat and light and drying and is very vulnerable in the presence of many common disinfectants, especially silver, either as nitrate or in loose organic combination.

It is probable that the organism has no natural habitat outside the bodies of human beings. The lower animals are not, as a rule, susceptible to inoculations of the mucous membranes with the gonococcus, but suppurative inflammation has been induced in mice and guinea-pigs by intraperitoneal injections. In man there are at least ten strains, immunologically speaking, which, however, do not differ appreciably in culture.[2]

Inoculations of pure cultures of the gonococcus upon the urethral mucous membranes of man have been repeatedly made and are followed by a characteristic catarrhal inflammation. Thus the evidence is complete that the gonococcus is an excitant of the inflammation with which it is so constantly associated. But in what measure this germ, in what measure others which may be associated with it, are responsible for the complicating inflammations, is yet to be determined. The gonococcus appears to act rather through its endotoxins or, more correctly, decomposition products, than by soluble substances set free in its growth.

Inasmuch as one or more forms of cocci and diplococci occurring in the normal and in the inflamed urethra are morphologically similar to the gonococcus, great caution should be exercised in doubtful cases in deciding upon the nature of suspicious microorganisms in urethral discharges or other exudates. But the pronounced tendency of the

[1] *Vedder, E. B.*, Jour. Infect. Dis., 1915, xvi, 385.

[2] *Torrey, J. C.*, Jour. Med. Research, 1907, N. S. xi, 329; *Teague* and *Torrey*, ibid., 1907, N. S. xii, 223.

gonococcus to gather within cells; the sometimes conspicuous but often ill-defined flattening of the apposed sides of the gonococci; the decolorization by Gram's method, which leaves most other germs apt to be associated with the gonococcus still stained, and whenever practicable the artificial-culture characters—these all should be considered in the summary of evidence.[1]

Recently the technique of a complement fixation test has been successfully developed.[1] In acute cases, the fixation test does not become positive until about six weeks have elapsed; indeed, with an uncomplicated anterior urethritis it may never appear. With deeper lesions, such as vaginitis in children, cervicitis, or salpingitis, or in invasion of vesicles or prostate, the reaction is positive in a large proportion of cases. In arthritis 100 per cent. of positive reactions have been reported. The diagnostic and medicolegal importance of the test is thus very great.[2]

ACUTE CEREBROSPINAL MENINGITIS.

This is an acute infectious process of which the characteristic lesion is an exudative inflammation of the pia mater of the brain and cord.

As a rule the inflammation of the pia mater results in the production of serum, fibrin, and pus, which infiltrate the pia mater and accumulate in the ventricles, so that the gross appearance of the brain is characteristic. The exudation is often especially abundant at the base of the brain and over the posterior surfaces of the cord. In children the distention of the lateral ventricles with purulent serum may be a marked feature, while in adults the quantity of serum is apt to be small. (For details of the lesions in exudative meningitis see Nervous System.)

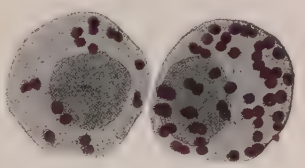


Fig. 135.—Diplococcus Intracellularis—Meningococcus.

From fluid obtained by spinal puncture in case of epidemic cerebrospinal meningitis.

While the above are characteristic lesions of this disease, there are a number of secondary or associated septicemic or toxemic lesions in different parts of the body. There may be subserous punctate hemorrhages in the endocardium; petechiæ in the skin; acute arteritis; hyaline and granular degeneration in the voluntary striated muscle; occasional multiple abscesses in various parts of the body; suppurative inflammation of the joints; albuminous degeneration of the heart, liver, and kidneys; and hyperplasia of the gastrointestinal lymphatic apparatus and of the spleen.

Cerebrospinal meningitis may occur by itself or in connection with some other acute infectious disease, such as acute lobar pneumonia, mycotic ulcerative endocarditis, pyemia, multiple suppurative arthritis, otitis media, puerperal fever, typhoid fever, etc.

[1] For summary of studies on the gonococcus with bibliography, consult *Koch* and *Bruck*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 655, 721.

[2] For details of the technique, see *Schwartz* and *McNeil*, Am. Jour. Med. Sc., 1911, cxli, 693; 1912, cxliv, 369, 815; and *Kolmer*, Infection, Immunity, and Specific Therapy, 2d ed., Philadelphia, 1917, p. 503.

It may be *epidemic*, the lesions, however, being essentially similar to those in the simple acute form.

The *bacterial excitants* of simple sporadic cerebrospinal meningitis are most commonly the pneumococcus and Streptococcus pyogenes. Of less frequent occurrence in the lesions are the influenza bacillus,[1] the typhoid bacillus, and the gonococcus. Other bacteria have been recorded.

Epidemic Cerebrospinal Meningitis.—This form of exudative inflammation of the meninges of the brain and cord is induced by an organism named by Weichselbaum *Diplococcus intracellularis meningitidis* (*meningococcus*) because of its form and its frequent presence within cells of the

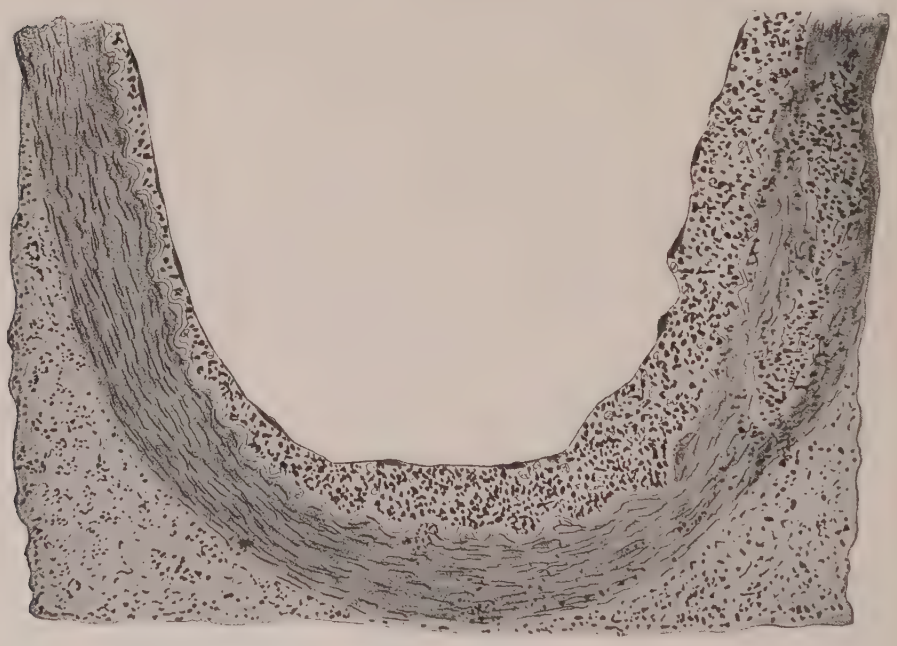


Fig. 136.—Acute Endarteritis and Arteritis in Epidemic Cerebrospinal Meningitis.

The endothelium is raised from the membrana elastica by an accumulation of cells—shown in the next figure. The muscularis is also involved.

exudate (Fig. 135). While often occurring in epidemics, infection with the meningococcus may be sporadic.

The lesions are in general similar to those above described in exudative inflammation of the meninges with other excitants, but, in distribution and type, present some moderately characteristic appearances. The exudate, which is purulent, seropurulent, or fibropurulent, is usually most marked at the base of the brain and on the posterior surface of the cord. In death at an early period there may be simple hyperemia with little exudate. The purulent exudate consists largely of polymorphonuclear leucocytes, but there may be large polyhedral

[1] See *Moore*, Brit. Med. Jour., 1913, ii, 1056 (bibl.).

cells mingled with them. These large cells, apparently derivatives of endothelium, are phagocytic and may contain leucocytes, red blood-cells, etc. At later periods these large cells may preponderate in the exudate. The exudate may be present in the superficial layers of the brain and may involve the cranial nerves and the spinal nerve roots. There may be proliferation of neuroglia cells.[1] Acute arteritis with the accumulation of leucocytes and the formation of new cells beneath the endothelium of the small arteries of the brain and cord (Figs. 136 and 137) is often present in this disease.

In the prolonged, so-called chronic cases there may be edema and thickening of the pia mater and degeneration of the pus cells.

Characters of Diplococcus Intracellularis Meningitidis.

It is a diplococcus, considerably resembling the gonococcus, the pairs and tetrads being often flattened on the apposed sides. It is non-motile, not staining by Gram's method. It grows readily though not voluminously on appropriate culture media at body temperature. It is readily killed by exposure to sunlight, and by drying as well as by heat, cold, and the common disinfectants. There are a number of varieties separable by their serum reactions.

While the meningococcus is most abundant in the meningeal exudate, and is obtained on lumbar puncture, it has been found in the blood[2]

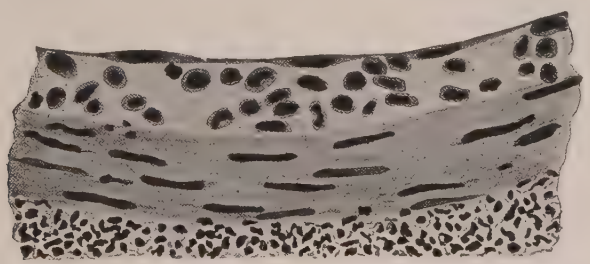


Fig. 137.—Endarteritis in Cerebrospinal Meningitis—Epidemic.
Leucocytes and polyhedral cells have gathered between the endothelium and the muscularis in this small artery.

and in the nasal passages. Agglutinative substances are formed during the infection.

Pathogenicity.—Inoculations of cultures into various animals, mice, rabbits, guinea-pigs, etc., show that it is moderately pathogenic, the effects seeming to be due largely to an endotoxin. Flexner has induced in monkeys lesions almost identical with those of man.[3]

Source.—The frequent occurrence of the meningococcus in the nasal passages both in those suffering from epidemic cerebrospinal

[1] For an epitome of lesions, see *Councilman*, Jour. Am. Med. Assn., 1905, xliv, 997.

[2] *Elser* and *Huntoon*, Jour. Med. Research, 1909, N. S. xv, 377 (bibl.); *Davis*, Jour. Infect. Dis., 1907, iv, 558; and *Baeslack, F. W.*, and others, Jour. Am. Med. Assn., 1918, lxx, 684.

[3] See *Flexner*, Tr. Assn. Am. Phys., 1906, xxi, 378; also Jour. Exper. Med., 1907, ix, 105 and 142.

meningitis at an early period and in those closely associated with them,[1] while it is usually absent in well persons not exposed to the disease, leads to the conclusion that the infectious material may be transmitted by the nasal secretion directly, or through the air in the spray caused by sneezing. Recent English statistics have shown that 10 per cent. of contacts may become carriers for from four to six weeks; in exceptional instances, the condition may persist for a year or more.[2] There is reason for believing that entrance is gained through the nasopharyngeal mucous membrane,[3] and through the pharyngeal tonsil. This is obviously possible through the direct connections which exist between the meninges and the nasal mucosa by lymphatics which pass the cribriform bone with branches of the olfactory nerve. But the possibility of origin through the blood is to be held in mind.[4]

Serum Therapy.—By the immunization of horses with dead and living cultures of various types of meningococcus, and with extracts of the bodies, polyvalent curative sera have been prepared.[5] Such sera injected intraspinously have been found after critical tests on a large number of cases to be extremely valuable curative agents.[6]

Micrococcus Catarrhalis.

Diplococci resembling the meningococcus and called *M. catarrhalis* have been found on respiratory mucous membranes. Their cultural characters are quite similar to those of the meningococcus, for which they may be easily mistaken. They are believed to be incitants of catarrhal inflammations. They are often associated with pneumococcus and the influenza bacillus. *Micrococcus flavus* is also a frequent inhabitant of the nasopharynx, and as it is gram-negative, like the meningococcus and the Micrococcus catarrhalis, must be carefully distinguished by culture.[7]

GLANDERS.

Glanders is an infectious disease incited by the presence and growth in the body of the *Bacillus mallei.*

It is most common in the horse, affecting the mucous membrane of the nose (when involving the skin the disease has been called *farcy*), and can be communicated to man and to certain other of the domestic animals by direct or accidental inoculations.

Man is quite susceptible to glanders infection, and the disease is most frequent in those who come much into direct contact with horses. The seat of primary local infection is most often the skin, more rarely the mucous membranes about the nose and mouth.

The local lesions are similar in man and the lower animals. In the

[1] See *Weichselbaum* and *Ghon*, Wien. klin. Wchnschr., 1905, xviii, 625; *Goodwin* and *v. Sholly*, Jour. Infect. Dis., 1906, Suppl. No. 2, p. 21; also *Elser* and *Huntoon*, Jour. Med. Research, 1909, N. S, xv, 377 (bibl.). For study of carriers, see *Chapin*, Sources and Modes of Infection, 2d ed., New York, 1912.

[2] See, for general review, *Flexner*, Jour. Am. Med. Assn., 1917, lxix, 639.

[3] *Westenhoeffer*, Berl. klin. Wchnschr., 1905, xlii, 737.

[4] For a study of cases with bibl., consult *Councilmann*, *Mallory*, and *Wright*, Special Report of the State Board of Health of Massachusetts, 1898; also *Elser*, Jour. Med. Research, 1906, N. S. ix, 89. For agglutinative reaction, see *Jaeger*, Ztschr. f. Hyg. u. Infectionskrankh., 1903, xliv, 225.

[5] *Kolle* and *Wassermann*, Deutsch. med. Wchnschr., 1906, xxxii, 609; *Jochmann*, ibid., 788, who first reported good results from intraspinous injections; *Flexner* and *Jobling*, Jour. Exper. Med., 1908, x, 141.

[7] *Flexner*, Jour. Am. Med. Assn., 1909, liii, 1443; 1912, lix, 1371.

[6] For methods, see *Flexner*, Jour. Am. Med. Assn., 1917, lxix, 639.

presence of the Bacillus mallei there is usually a circumscribed or more rarely a diffuse infiltration of the tissue with leucocytes and young connective-tissue cells. These whitish foci of cell accumulation may be small and to the naked eye resemble miliary tubercles, or they may be larger and nodular. The tissues about them may be infiltrated with blood. But the accumulated cells are apt, in the presence of the bacilli, to become necrotic and disintegrate and thus lead to smaller and larger abscesses, or, if near the surfaces, to ulcers. If they occur on mucous membranes these lesions are often accompanied by intense diffuse catarrhal inflammation.

As the glanders nodules soften, the bacilli are apt to diminish in number or in the capacity to stain, so that it may be possible to detect their presence only by inoculation or culture methods.

The disease may begin at a single point, so that it may be mistaken for a carbuncle or gangrenous erysipelas. But the infection is apt not to remain local; the bacilli, finding their way along the lymph-channels into various parts of the body, set up fresh foci of inflammation and necrosis. Then the skin may be covered with a pustular eruption; furuncles, carbuncles, and abscesses may form beneath the skin and in the muscles. Nodules are found in the nasal mucous membrane, the lungs, kidneys, testes, spleen, and liver. The joints may be inflamed, and there may be osteomyelitis. Leucocytosis may accompany infection with the Bacillus mallei.

The glanders infection may, however, pursue a more chronic course, with hard, persistent nodules and sluggish ulcers. Under these conditions the detection of the bacillus in the tissue by a simple morphological examination may be difficult.

While some forms of glanders nodules somewhat resemble in gross and microscopic appearance certain forms of miliary tubercles, the absence in the former of coagulation necrosis and of giant cells, and the tendency to rapid disintegration and softening in the latter, will usually suffice for the distinction between the two sets of lesions. But the demonstration of the bacilli characteristic of each is in all cases decisive.

Characters of the Bacillus mallei.—The Bacillus mallei is a slender bacillus proportionately thicker than the tubercle bacillus, with rounded ends, occurring singly or in pairs (Fig. 138). It stains easily with the aniline dyes, but readily gives up the color in presence of even feeble decolorizing agents such as dilute alcohol or acids. It is left decolorized by Gram's method.

It is non-motile, does not form spores, and frequently shows vacuoles and various involution forms.

In the tissues the bacilli may be stained with Loeffler's alkaline methylene blue.

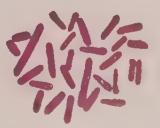


Fig. 138.—Bacillus Mallei.

The glanders bacillus grows readily on almost all of the ordinary artificial culture media, and best at blood heat. The growths on solid media are apt to be viscid. On potato it forms in two or three days an abundant yellowish pellicle which in a few days darkens and finally becomes brown in color. It gradually loses its virulence in successive generations of artificial cultures. The germ is easily killed by moist heat, by sunlight, drying, and the several germicidal chemicals.[1]

[1] For a résumé of characters of the glanders bacillus see *Wladimiroff*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 1063.

Field mice and guinea-pigs are very susceptible to infection with the Bacillus mallei, and develop highly characteristic local and general lesions.

Toxic Products and Immunity.—The toxic product of B. mallei is chiefly stored in the body of the organism as an endotoxin. On extraction by methods similar to those used in the preparation of tuberculin (page 300), a substance called *mallein* has been produced, and has been found useful as a means of diagnosis in glanders, affected animals showing local reactions and a sharp rise of temperature, and marks of toxemia.

Immunity is not apparently secured by glanders infection and while antibodies—agglutinins—are formed, effective curative sera have not been prepared.

Diagnosis.—In cases in which an early diagnosis is imperative it is well, in addition to the morphological examination and cultures of the suspected exudate, to inject a small amount into the peritoneal cavity of a male guinea-pig. If the virulent glanders bacilli be present, within two or three days the testicles will swell and develop an intense suppurative inflammation.

Other Bacilli Related to Bacillus Mallei.

Several bacilli, apparently related to the B. mallei, have been found in various lesions in men and lower animals. Thus an organism called *Bacillus pseudotuberculosis* has been found in certain nodular lesions somewhat resembling tubercles which are especially frequent in rodents. *B. pseudotuberculosis liquefaciens* has been described in a series of cheesy nodules of the peritoneum, pancreas, and liver in man. In this group also belong organisms which have been found in noma.

Chancroid (Soft Chancre).

Soft chancre or chancroid is an acute inflammatory lesion usually of the genital regions, at first pustular, then ulcerative. The infective agent is communicated by contact. Neighboring lymph-nodes are apt to suffer an acute hyperplasia passing into abscess.

In the lesion of *soft chancre* and the discharge from it a small oval bacillus ("Ducrey's bacillus") has been frequently found either clustered or in chains. It stains readily with methylene blue, although it easily loses the color. It usually occurs with other microorganisms, and has been found, though not commonly, in the buboes. It has been obtained in pure culture in rabbit-blood agar and in human blood, and inoculation experiments in man and in monkeys indicate its pathogenicity.[1]

ANTHRAX. (Splenic Fever; Malignant Pustule; Charbon; Carbuncle.)

This disease, which is much more common in the lower animals, especially the herbivora, than in man, is widely prevalent in Europe. It is comparatively rare in the United States, but in certain regions is more common than formerly.

It is induced in man by accidental inoculation with the Bacillus anthracis, which also incites the disease in the lower animals. Inoculation may occur through the skin by the agency of flies and other insects which have been feeding on animals infected with this disease, through abrasions or slight wounds on the hands of those handling their carcasses or hides, or in other ways. Following this skin inoculation a pustule is apt to develop—"malignant pustule"—and varying phases of an acute exudative inflammation, which may be hemorrhagic, serofibrinous, purulent, or necrotic, accompany the local proliferation of the germs (Fig. 139). Anthrax bacilli in large numbers may be present in the local lesion. From this local source a general infection may ensue. General infection may occur without evident external lesion.

[1] See *Davis, L.*, Jour. Med. Research, 1903, N. S. iv, 401 (bibl.).

Infection with anthrax may occur through the lungs, most often among those who handle infected wool or hides, the dust from which is inhaled ("wool-sorter's disease"). Under these conditions there may be edema and lobular pneumonia with involvement of the pleura, mediastinum, and other adjacent structures. Infection through the gastro-intestinal canal takes place by the ingestion of food containing anthrax spores, and is apt to be accompanied with inflammatory and necrotic changes, which are described in detail among lesions of the intestine. This is a common mode of infection in animals.

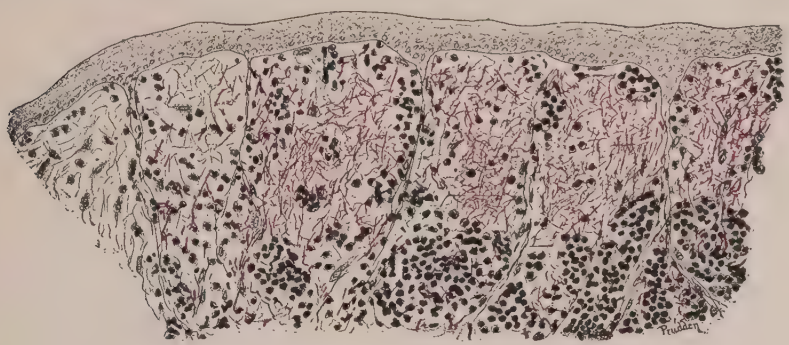


FIG. 139.—ANTHRAX—MALIGNANT PUSTULE—OF THE SKIN.
From a man who had been handling foreign hides in New York. Bacilli stained.

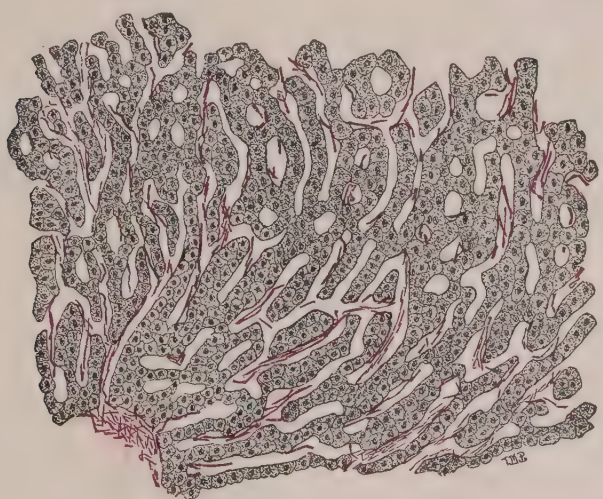


FIG. 140.—BACILLUS ANTHRACIS GROWING IN THE BLOOD-VESSELS OF THE LIVER OF A MOUSE INOCULATED WITH A PURE CULTURE OF THE BACILLUS.

When general anthrax infection occurs the post-mortem appearances vary. Decomposition, as in other acute infections, generally sets in early. The blood is frequently not much coagulated and dark in color. Hemorrhages and ecchymoses are frequently found in the serous and mucous membranes and in various other parts of the body.

The lungs may show small hemorrhages and edema, and the bronchi may be deeply congested. The pleural cavities may contain serum. The intestines may exhibit the lesions of the so-called *intestinal mycosis.* The bronchial and other lymph-nodes may be swollen. The spleen may be swollen, very dark in color, and soft, sometimes almost diffluent.

The bacillus may be found, usually in large numbers, in the spleen and in the capillary blood-vessels, especially in the liver (see Fig. 140), lungs, kidneys, and intestines.[1] A serum which has some therapeutic value has been prepared;[2] but the use of normal beef serum has apparently yielded equally good results.[3]

Characters of the Bacillus Anthracis.

The Bacillus anthracis is from 5 to 20 μ long and about 1 to 3 μ broad, and is often uneven along the sides. The ends of the bacilli are square or slightly concave, and the bacilli often hang together end to end, forming thread-like structures (Fig. 141). While the bacilli in the vegetative condition are easily killed, they develop spores outside the body only, and these are very invulnerable to the ordinary germicidal agents and to heat, resisting often for many days the action of from 2 to 5 per cent. carbolic acid and defying for some minutes the action of live steam. Anthrax bacilli are immobile, sometimes capsulated, and are easily stained by the aniline dyes. They grow readily on artificial culture media at ordinary room temperatures, fluidifying gelatin.

Subcutaneous inoculation of cultures of the anthrax bacillus into various species of animals induces characteristic lesions. White mice and guinea-pigs are especially susceptible, usually succumbing to the anthrax septicemia in from two to four days. Serous exudations, often bloody and with many bacilli, develop at the seat of inoculation, while in the blood multitudes of the bacilli are found.

Immunization.—If cultures of the anthrax bacillus be made at a temperature of about 42° C., growth occurs, but it is meager. Spores are not formed as they are at body temperature, and the virulence of the germ diminishes day by day, so that at last the most susceptible animals are not affected by large inoculations of the living organisms. If fresh cultures of these organisms be made in various stages of their diminishing virulence and maintained at their optimum temperature, spores will again form, the growth will become vigorous, and in morphology quite characteristic; but the physiological qualities which determine virulence will remain more or less in abeyance.

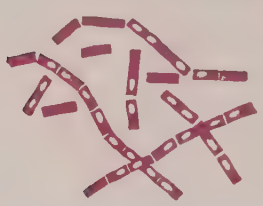


Fig. 141.—Bacillus Anthracis Containing Spores. From a culture.

By inoculation of animals with anthrax cultures, first with those which had been kept at 42° C. for from fifteen to twenty days, and thus had but feeble virulence, then passing to those cultivated at 42° C. for a shorter time and which were thus more virulent, Pasteur secured immunity from anthrax in a series of the lower animals (see p. 193). Based upon these experiments a method of protective inoculation has been practised on a large scale among sheep and other animals in some parts of Europe which has been of great economic value. The death rate from anthrax has by these methods been reduced in sheep from 10 per cent. to about nine-tenths of 1 per cent., and in cattle from 5 per cent. to less than four-tenths of 1 per cent.[4]

Little is known of soluble toxins or endotoxins of the anthrax bacillus.

[1] For bibliography and résumé of anthrax see *Sobernheim*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, iii, 583.

[2] *Brown* and *Simpson*, Jour. Am. Med. Assn., 1917, lxviii, 608.

[3] For a review of this method of treatment, see *Hyman, C. H.*, and *Leary, T.*, Boston Med. and Surg. Jour., 1918, clxxviii, 318.

[4] For a study of opsonic substances in dog serum favoring phagocytosis of anthrax bacilli, see *Hektoen*, Jour. Infect. Dis., 1906, iii, 102.

ACTINOMYCOSIS.

This disease, which is of occasional occurrence in man, but is more common in the domestic animals, especially in cattle and in horses, is most frequently characterized by a slow suppurative and proliferative process, often leading to the formation of large fungous masses which may become calcareous.

In cattle, the new-formed tissue, which develops with especial frequency in the jaw, is apt to extend beyond the original site and to slough, so that not only may the tissues of the tongue, pharynx, larynx, etc., be involved, but secondary nodules of similar character may form in the lungs, gastrointestinal tract, and skin.

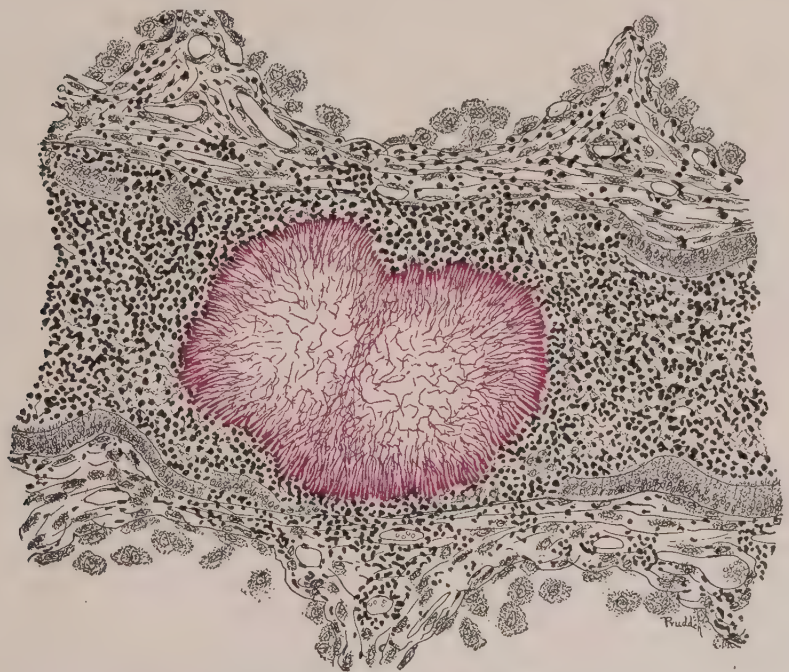


FIG. 142.—ACTINOMYCES GROWING IN HUMAN BRONCHUS.
(The bulbed ends of the filaments are seen in the borders of the colony. The bronchus, cut lengthwise, contains purulent exudate, and its wall is becoming involved.)

In man, suppuration with necrosis and the formation of abscesses, ulcers, and fistulæ, are the most marked lesions in parts near the surface of the body. In the *lungs* the lesions may be essentially those of an acute general bronchitis or in the form of bronchopneumonia (Fig. 142), with the formation of new tissue.[1]

Abscesses and cavities may form which extend into adjacent parts. In intestinal actinomycosis nodular masses of new tissue with ulceration may develop in the mucosa and submucosa. Metastases have been described. The excitant of this disease—now most commonly called

[1] For a detailed description of the lung lesions in actinomycosis, see *Hodenpyl*, Med. Rec., 1890, xxxviii, 653 (bibl.).

Actinomyces bovis—is a microorganism which seems to be more closely related to the moulds than to the bacteria. It is, however, considered here because its botanical position is not yet clearly established, and it may be one of the so-called pleomorphous bacteria (see page 165).

The organism often grows in the tissues in the form of little rounded masses from a size so small as to be invisible to that of a pin's head. They may be transparent or grayish white or yellow or dark in color. Under the microscope these masses often appear in the form of a dense group of radiating filaments with more or less bulbous ends; hence the common name "ray fungus."

Characters of Actinomyces.

The organism when freed from other bacteria is readily cultivated at 37° C. It grows in delicate branching threads which show segments resembling bacilli and cocci besides bulbous or club-shaped forms, probably "involution forms." Successful inoculations of cultures have been made in animals.

The organism is usually conveyed from one animal to another by inoculation or by contact of the growth with a wound or an abrasion of the mucous membrane.

In the examination of sputum, feces, pus, etc., for the presence of actinomyces the naked-eye appearances may be of value, since the yellowish white granules are often quite visible, especially on a black background. Suspicious masses may be teased and studied unstained, or stained by Gram's method. Blocks of tissue may be hardened in alcohol, and sections stained by Gram's method with contrast eosin stain.

Other Organisms Resembling Actinomyces.

Many forms of microorganisms of similar general characters to actinomyces have been described, some occurring in connection with infective processes in man and the lower animals, of which they seem to be the excitants, others living as saprophytes in various situations. Among the apparently pathogenic forms we may mention the following:

An organism somewhat resembling actinomyces and found in connection with a disease commonly called mycetoma or "Madura foot," frequent in the tropics and characterized by nodular growths associated with suppuration and necrosis most often affecting the foot.[1]

Another form has been described in connection with a peculiar form of erysipelatous inflammation of the skin; another in the so-called *farcin de bœuf*, a disease of cattle in Guadeloupe; this has been called *Streptothrix* and now *Nocardia*.

Several times organisms of this general character, but differing considerably from actinomyces, have been found in inflammatory and necrotic lesions of the lungs. Whether these are variants of that species or independent species, and how many such there are it is impossible at present to say.[2] Many attempts have been made to classify these organisms but knowledge of them is still too incomplete to permit accurate distinctions.

[1] Consult *Wright, J. H.*, Jour. Exper. Med., 1898, iii, 421 (bibl.); Jour. Med. Research, 1905, N. S. viii, 349; and Osler's Modern Medicine, 1907, i, 327; and *Babes, V.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 365.

[2] For a description of two such cases, with a selected bibliography, see *Norris* and *Larkin*, Jour. Exper. Med., 1900, v, 155; also case by *Tuttle*, Med. and Surg. Rep., Presby. Hosp., New York, 1904, vi, 147.

For a critical summary of this group of organisms, with a full bibliography, see *Lachner-Sandoval*, Ueber Strahlenpilze, Strasburg, 1898; also *Petruchsky*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 267; *Schlegel*, ibid., p. 301; and *Musser, Pearce*, and *Gwyn*, Tr. Assn. Am. Phys., 1901, xvi, 208.

Sporotrichosis.

In the last few years a considerable number of cases of a chronic fungoid process involving the skin and mucous membranes, and occasionally resulting fatally, have been described. Several types of organism, growing on ordinary media, have been isolated. The condition is known as sporotrichosis.[1] (See also page 179.)

Pharyngomycosis Leptothrica.

Certain filamentous microorganisms called *Leptothrix*, whose botanical affiliations are not yet clear, are of common occurrence in the mouths of healthy persons. Occasionally, however, a persistently recurrent attack of "sore throat," with local tenderness and sometimes cough and fever, is associated with the growth of masses of leptothrix in the crypts of the tonsils, at the base of the tongue, on the walls of the pharynx, or in the nose or superior portion of the esophagus. The leptothrix masses or colonies form thick whitish pellicles or patches which may be superficial, or in tonsils may extend deep into the crypts. These masses are usually firmly adherent, often leave bleeding surfaces when removed, and the growth is apt persistently to recur.

Microscopic examination of removed portions of the growth show tufts and bundles of the thread-like microorganisms, growing among or directly out from flat epithelial cell masses and mingled with various other forms of microorganisms, mostly cocci and short bacilli. There may be overgrowth of epithelium and collections of leucocytes in and about the leptothrix masses.[2]

INFLUENZA. (Epidemic Catarrhal Fever; La Grippe.)

This is an infectious disease characterized by fever, physical and mental prostration, and exudative inflammations in different parts of the body. Thus there may be exudative inflammation in the respiratory, digestive, and nervous systems, either singly or together. Sometimes, however, these local inflammations may be absent, when the disease may be marked by the characteristic prostration and symptoms of toxemia. None of the lesions appear to be characteristic. The lesion of the lungs is usually of the bronchopneumonic type and is apt to involve the interstitial tissue. The cut surface is smooth, the exudate is soft and contains relatively little fibrin. The lung resembles that of "purulent infiltration."

The numerous bacterial studies which up to 1892 had been made on epidemic influenza had failed to reveal any microorganism which could fairly be regarded as of etiological significance, although some of the complicating inflammations of the lungs had been shown to be very frequently associated with the pyogenic cocci—Staphylococcus pyogenes and Streptococcus pyogenes and the Diplococcus pneumoniæ.

Early in 1892, Pfeiffer, Kitasato, and Canon described the occurrence in the bronchial exudate and in the blood of influenza patients of a very small bacillus, hitherto unknown or possibly noted earlier by Babes. This bacillus—*B. influenzæ*—is sometimes present in the bronchial exudate in enormous numbers, and often with little or no contamination with other germs. It is found at the seat of other local lesions, and the pus cells often contain many bacilli. It has been found to persist in the body long after the active processes have ceased.[3]

[1] *de Beurmann* and *Gougerot*, Traité des sporotrichoses, Paris, 1912.

[2] For further details, and bibliography, consult *Campbell*, Med. News, 1896, lxviii, 371; also *Pearce*, Bull. Univ. Pennsylvania, 1901, xiv, 217; and *Davis, J. D.*, Jour. Infect. Dis., 1914, xiv, 144.

[3] For a full résumé of the characters of the influenza bacillus and its relation to various forms of the disease, with bibliography, see *Scheller, R.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 1257. See also, *Vaughan, W. T.*, Influenza, Amer. Jour. Hygiene, Monographic Ser., No. I, July, 1921; and *Winternitz, M. C., Wason, I. M.*, and *McNamara, F. P.*, The Pathology of Influenza, New Haven, 1922.

Characters of the Influenza Bacillus.

The influenza bacillus is very small—about 0.5 μ long by 0.2 to 0.3 μ in width—with rounded ends, non-motile, and does not form spores. It stains with some difficulty with simple aniline dyes; but by Ziehl's solution, or by warmed Loeffler's methylene blue it is readily colored. It does not retain the stain well by Gram's method. The organism apparently dies after a few hours' drying in the air and soon in water and is readily killed by heat or cold or chemical germicides.

This bacillus grows best at body temperature, on glycerin-agar whose surface has been smeared with blood—human, rabbit, or pigeon. It forms very small, scarcely visible, dewdrop-like colonies, which, although growing close together, do not tend to coalesce, as those of many microorganisms do. It has been cultivated through several generations, but usually dies soon.

The evidence that the organism described above is the excitant of epidemic influenza rests largely upon its apparently constant presence, especially in the exudates of the nasal and bronchial mucous membranes, where it may be present in enormous numbers and almost free from admixture with other germs.

Cases of sporadic influenza are of frequent occurrence, especially in towns. These are often mixed infections, the influenza bacillus being associated with pneumococcus, streptococcus, etc.

That the organism should have been occasionally found under other conditions,[1] as in chronic pulmonary tuberculosis, does not at all militate against its significance in inciting the manifestations of influenza, since many parallel instances are known in other infectious diseases. The frequent discrepancy between the clinical and bacterial diagnosis in influenza is largely due to its varying and often obscure clinical manifestations which render possible and convenient the use of the name for many phases of catarrhal and other forms of inflammation.

Immunity in any marked degree does not appear to be conferred by influenza.

During the recent influenza epidemic, encephalitis lethargica became very frequent, and it has been suggested that there is some correlation between the two diseases, possibly on the basis of a filterable virus, but nothing definite has been discovered.

In 1920 Olitsky and Gates[2] found in the naso-pharyngeal washings of influenza patients during the first 36 hours of the disease a filter-passing agent, mildly pathogenic for rabbits if administered intratracheally. The lesions in the rabbit were practically confined to the blood and pulmonary systems—a marked leucopenia, characterized by decrease in the mononuclears; while congestion, edema and sub-pleural hemorrhages were the marked features. The agent itself did not cause death of the animals, but a marked lowering of the resistance to pulmonary infections with ordinary bacteria.

This agent, identified as Bacterium pneumosintes, passes Berkefeld filters V and N, and can be grown in certain enriched media. It is a small coccobacillus, measuring from 0.15 to 0.3 micra in its long axis and Gram negative. Of itself it causes relatively mild disease with a marked predisposing action toward infection with ordinary bacteria in the pulmonary system.

[1] See *Park* and *Williams*, Pathogenic Microorganisms, 8th ed., New York, 1924, p. 465; see also for studies of this organism *Lord*, Boston Med. and Surg. Jour., 1905, clii, 537, 574; *Auerbach*, Ztschr. f. Hyg. u. Infectionskrankh., 1904, xlvii, 259; and *Davis*, Jour. Infect. Dis., 1906, iii, 1.

For a study of the influenza bacillus in inflammations of the respiratory tract in infants, see *Wollstein, M.*, Jour. Exper. Med., 1906, viii, 681.

[2] *Olitsky* and *Gates*, Jour. Exp. Med., 1922, xxxvi, 501, gives a summary of previous work.

Bacterium pneumosintes has been reported from influenza cases from practically every part of the world.[1] It is said to be found only in persons suffering from influenza and to be present only in the first stages of the disease. Besides this organism three groups of filter-passing bacteria have been found that may also occur in normal individuals and are not pathogenic to rabbits.

Pfeiffer[2] does not believe that the evidence indicates that Bacterium pneumosintes has replaced the influenza bacillus in importance as an etiological factor in influenza. Evidently the whole question of the causation of influenza is still unsolved.

TYPHOID FEVER.

Typhoid fever is an acute infectious disease incited by the *Bacillus typhosus*. The reaction of the body to this bacillus is usually manifested by characteristic lesions, especially by hyperplasia and necrosis in the lymphatic structures of the intestines and the mesenteric lymph-nodes, and in the spleen, as well as by the more general alterations incident to toxemia and septicemia; but the infection is occasionally of the septicemic type without characteristic local lesions in the intestines, or mesenteric nodes, or other viscera.[3]

The Bacillus of Typhoid Fever.

The presence of a bacillus, called Bacillus typhosus, in various parts of the body in typhoid fever, in a considerable proportion of the cases examined, has been well established. This bacillus does not occur in the body, so far as is known, except in connection with this disease, although it may persist in the gall-bladder or intestine for years after convalescence.

Characters of the Bacillus Typhosus.

The typhoid bacillus is usually about three times as long as broad, being about one-third as long as the diameter of a red blood-cell. It is rounded at the ends, motile, aerobic, facultative anaerobic and asporogenous. It grows readily at room temperature on the ordinary media. In cultures the bacilli often cling together end to end, forming threads (Fig. 143). It is readily killed by heat, is fairly resistant to chemical germicides, and remains alive for some time frozen in ice.

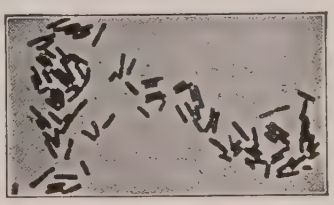


Fig. 143.—Bacillus Typhosus.

The inoculation of lower animals with the typhoid bacillus may result in various lesions, and prove fatal, but typical typhoid fever is not induced.[4]

The typhoid bacillus in its growth in cultures does not seem to produce soluble toxins of marked potency in very considerable amount though there is evidence that some such poison is formed.[5] On the other hand, there is stored up in the bodies of the bacilli a virulent endotoxin which has been largely used in artificial immunization.

[1] *Gates*, Jour. Exp. Med., 1926, xliv, 787.

[2] *Pfeiffer*, Deutsch. med. Wochnschr., 1925, li, 10.

[3] For studies on various phases of typhoid infection, see Johns Hopkins Hospital Reports, 1900, viii.

[4] For a study of experimental typhoid, see *Atlassoff*, Ann. Inst. Pasteur, 1904, xviii, 701 (bibl.).

[5] For a study of the soluble poisons of the typhoid bacillus, see *Rodet, Lagriffoul*, and *Aly Wahby*, Arch. de méd. expér., 1904, xvi, 397.

It is probable that the more characteristic symptoms and lesions of typhoid fever are largely due to the absorption of toxic substances which are produced as the result of the life processes of the bacteria at the point of their greatest accumulation and activity. It should be borne in mind that the typhoid bacillus, as is the case with many other bacteria, may induce local changes by means of its endotoxins, which are set free as the organisms disintegrate after their death in the body.[1]

Primary Characteristic Lesions.

We shall first consider the lesions which are most common and characteristic of typhoid fever.

The Intestines.—The lesions of the intestines consist of an inflammatory enlargement (hyperplasia) of the solitary lymph-nodules and of the agminated lymph-nodules (Peyer's patches). Necrosis of the nodules with ulceration frequently follows the hyperplasia.

The process appears to begin with a catarrhal inflammation of the mucous membrane, accompanied or immediately followed by changes in the lymph-nodules. The lesions in the lymph-nodules begin early;

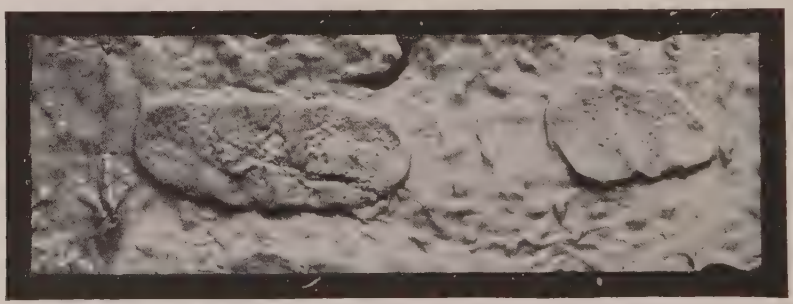


Fig. 144.—Hyperplasia of Peyer's Patches in Typhoid Fever.

they have been observed in persons who have died forty-seven hours after the commencement of the disease. The increase in size of the agminated and solitary nodules may be rapid or gradual. The nodules may be only slightly enlarged, or may project far into the lumen of the intestine. The enlargement is usually more marked in the agminated than in the solitary nodules. Usually the whole of a Peyer's patch is enlarged, but sometimes only a part of it. If the enlargement be gradual the different nodules which make up a Peyer's patch may enlarge, while the septa between them remain but little changed, thus giving the patch an uneven appearance.

The patches which are only moderately enlarged are of reddish or reddish gray color, and soft and spongy, and their edges blend gradually with the adjoining mucous membrane. The patches which are more markedly affected are of grayish color, of firm consistence, and rise abruptly from the surrounding mucous membrane (Fig. 144) or even

[1] For a study of the typhoid bacillus with reference to the pathology, diagnosis, and hygiene of the disease, see *Hiss*, Med. News, 1901, lxxviii, 728.

overhang it like a mushroom. The largest patches are sometimes more than three-eighths of an inch thick.

The enlargement and infiltration may spread from the patches to the surrounding mucous membrane, so that the patches appear very large; a number of them may become fused together, and there may even be an annular infiltration entirely around the lower end of the ileum. The infiltration, limited at first to Peyer's patches, may extend outward into the muscular coat, and appear in the peritoneal coat as small, gray, rounded nodules. This condition is usually found only with a few patches in the lower end of the ileum; sometimes in the cecum and appendix vermiformis.

The solitary nodules are affected in the same way as Peyer's patches. They may be hardly enlarged at all, or be quite prominent, or may be affected over a larger portion of the intestine than are the patches. Very rarely the solitary nodules are enlarged, while the patches are not at all or but slightly affected.

The inflammation and enlargement of the agminated and solitary nodules may be followed by a healing process. The character of this process varies according to the intensity of the previous inflammation.

If the reaction be slight and the enlargement of the nodules moderate, the enlargement gradually disappears, and they resume their normal appearance (resolution). In moderate enlargements of Peyer's patches resolution proceeds first in the nodules, leaving the septa between them for a time still swollen and prominent. This gives to the surface of a patch a reticulated appearance. After a time, however, the entire patch becomes flattened and uniform. On the other hand, the solitary nodules or the separate nodules of a patch may soften and break down, and their contents be discharged with some attendant hemorrhage. This leaves a bluish gray pigmentation, due to altered hemoglobin, in the situation of each nodule, and this may remain for years.

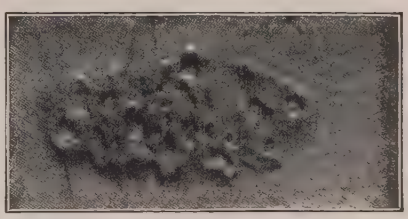


Fig. 145.—Hyperplasia of Peyer's Patch in Typhoid Fever, with Small Ulcers.
The separate small ulcers are extending and have in part coalesced.

In more severe types of the disease the enlargement of the nodules and Peyer's patches ends in ulceration. This takes place in two ways:

(*a*) The enlarged nodules or patches become necrotic, soften, break down, and discharge into the intestine. In this way are formed small ulcers (Fig. 145). These ulcers increase in size by the same softening process, which gradually extends at their edges, and in this way ulcers of large size may be formed.[1] The ulcers may extend outward to the muscularis or to the peritoneal coat, or they may involve the peritoneal coat also and perforate.

[1] Owing to the frequent involvement of Peyer's patches, the larger intestinal ulcers in typhoid fever are apt to have their longest diameter lengthwise of the gut in contrast to spreading tuberculous ulcers, which, owing to the extension of the local inflammation along the encircling lymph-channels, are apt to have the longest diameter crossing the gut. But exceptions to this general rule are common.

(*b*) In the severest forms of the disease considerable portions of the enlarged patches may slough and become detached, leaving large ulcers with thick, overhanging edges (Fig. 146). The slough may involve only the nodules, or it may involve also the muscular and peritoneal coats, and perforation may occur. These ulcers also may afterward increase in size, and several of them may be joined together. When the ulceration leads to perforation, peritonitis and death are the usual result. In rare cases, however, the patient recovers and the perforation is closed by adhesions.

If the patient recover, the ulcers are covered by granulation tissue, their edges become flattened, the granulation tissue becomes firmer and denser, and this new connective tissue is gradually covered with cylindrical epithelium.

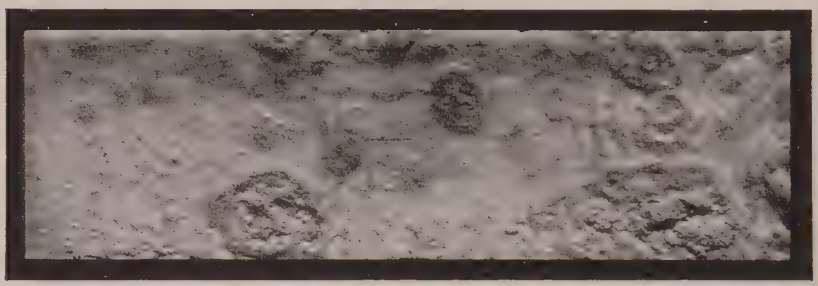


FIG. 146.—ULCERATION OF PEYER'S PATCHES AND SOLITARY LYMPH-NODULES IN TYPHOID FEVER. The swollen patches and nodules are necrotic except at their edges, the central portions forming a ragged slough.

The minute changes which take place in the development of the intestinal lesion are as follows:

At first the blood-vessels around the nodules are dilated and congested, while the nodules are swollen and the epithelium may fall off. Then the nodules increase in size, largely from a growth of new cells.

This cell growth is essentially a hyperplasia of normal elements of the lymphatic tissue, namely, the lymph cells and the endothelium of the trabeculæ and sinuses. There are thus two main types among the new-formed cells: first, small cells with relatively large and deeply staining nuclei; and second, larger polyhedral or rounded cells with more or less vesicular nuclei. The larger cells may contain foreign substances, such as red blood-cells or leucocytes (Fig. 147). The occurrence of mitotic figures in the endothelial cells while these are in situ, and the position and grouping of the large cells, appear to prove their endothelial origin. The production of new cells is not confined to the nodules, but extends also to the adjacent mucous membrane and underlying tissue. In many cases also little foci of similar new-formed cells are found in the muscular, subserous, and serous coats.

In this stage resolution may take place; then the new-formed cells degenerate and gradually disappear. In severer forms of the disease necrotic changes are apt to supervene, leading to the large and small

ulcers above described. The factors which determine the death of the hyperplastic tissues are not yet fully understood. It is believed by some to be directly due to toxic substances formed by the typhoid bacilli which kill the tissue cells; others are inclined to attribute it to the pressure which the new-formed cells exert on the nutritive blood-vessels.

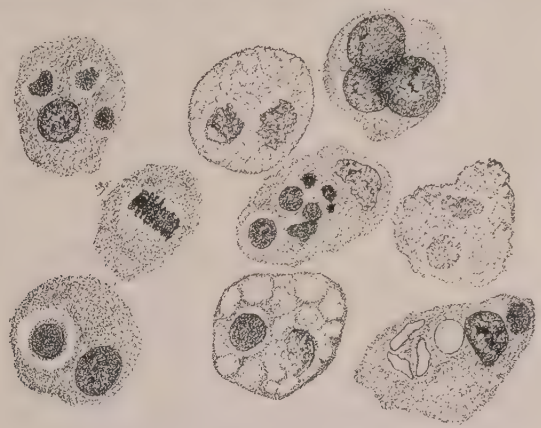


FIG. 147.—ENDOTHELIAL CELLS IN HYPERPLASIA OF PEYER'S PATCH IN TYPHOID FEVER.

These exfoliated and newly formed cells contain various foreign substances—leucocytes, red blood-cells, fragments of nuclei, etc. Some of them are necrotic and are degenerating. A mitotic figure is seen in one.

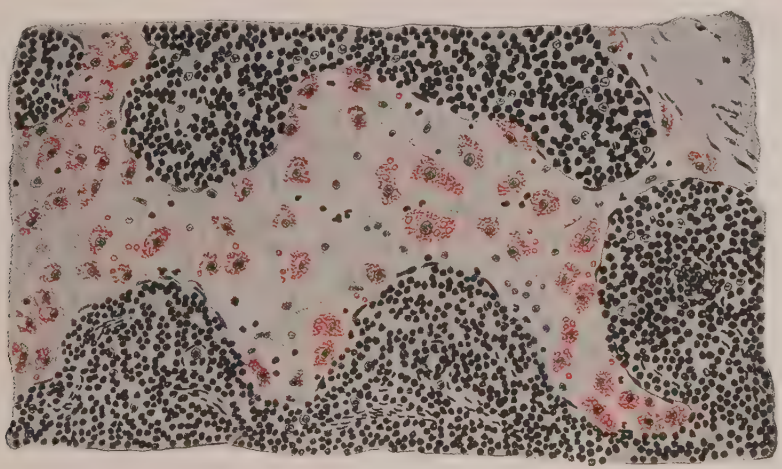


FIG. 148.—PHAGOCYTES IN THE PERIFOLLICULAR SINUSES OF A MESENTERIC LYMPH-NODE IN TYPHOID FEVER.

The large cells in the sinuses contain red blood-cells and blood pigment.

The conclusions on this point which Mallory draws from a long and interesting series of studies would indicate that a proliferation of the endothelial cells of the blood-vessels may lead to their occlusion. This observer describes the formation of occluding thrombi in the lymph-

vessels and smaller veins. These are composed of the proliferated endothelial cells which have degenerated, together with fibrin whose formation these degenerating cells induce. The accumulation of serous and fibrinous exudate about these thrombi, and the necrosis of tissue which may now ensue may soon be followed by necrosis of the superficial epithelium and the development of ulcers. The accumulation of polymorphonuclear leucocytes may, according to Mallory, now occur, and, in cases which go on to recovery, healing follows by the formation in the usual way of granulation tissue with the ultimate restitution of the surface epithelium. Mallory lays great stress upon the phagocytic nature of the new-formed cells of the veins and lymph-vessels (Fig. 148 and Fig. 149). For the significance of this process and other interesting details we refer to the original paper.[1]

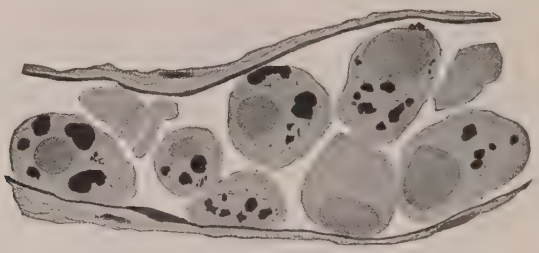


Fig. 149.—Phagocytic and Necrotic Cells in Lymph-vessel near Peyer's Patch in the Wall of the Intestine in Typhoid Fever.

The lesions which we have described are found most frequently and are most pronounced in the lower part of the ileum. They are not always, however, confined to this situation. Enlarged and ulcerated nodules may be found over the entire length of the ileum and even in the jejunum. They may also extend downward and be found in the colon, even as far down as the rectum. Similar changes may take place in the appendix vermiformis.[2] A few cases are recorded in which local nodular foci of new cell production, necrosis, and ulceration are limited to the colon. Clusters of typhoid bacilli may be found in these nodules. These are usually irregularly scattered, are not limited to a hyperplasia of the lymph-nodules, and should be distinguished from simple nodular hyperplasia with ulceration.[3]

Mesenteric Lymph-nodes.—The mesenteric nodes undergo changes similar to those in the nodules of the intestines, and are usually affected in a degree corresponding to the intensity of the intestinal lesion.

The nodes are at first congested and succulent; then there is a production of lymphoid cells and large cells as in the intestinal nodules, and the node becomes enlarged. When the enlargement has reached its full extent, congestion diminishes, and the cells begin to degenerate. The degeneration may take place slowly, and then the node gradually

[1] *Mallory, F. B.*, Jour. Exper. Med., 1898, iii, 611.

[2] For a study of the distribution of typhoid ulcers, see *Baer, J. W.*, Am. Jour. Med. Sc., 1904, cxxvii, 787. For record of cases in which the infection and the symptoms seemed to be confined to the appendix, see *Wolfsohn*, Berl. klin. Wchnschr., 1915, lii, 872.

[3] See *Whipple*, Bull. Johns Hopkins Hosp., 1906, xvii, 281.

returns to its normal condition; or more rapidly, and then little foci of necrotic, purulent material are formed. If the patient recover the small foci are absorbed, leaving a fibrous cicatrix; the larger foci may become dry, necrotic, and inclosed in a fibrous capsule. Intense exudative inflammation may occur in the nodes, which may be densely infiltrated with serum, fibrin, and pus.

The Spleen.—In nearly every case of typhoid fever the spleen is enlarged. This enlargement begins, as a rule, soon after the commencement of the disease, increases rapidly until the third week, remains stationary for a few days, and then diminishes. The organ is congested, of dark red color, and of firm consistence while it is increasing in size. After it has reached its maximum size, its consistence becomes soft, and there is a considerable deposit of brown pigment. The enlargement appears to be due to congestion and hyperplasia.

Mallory describes proliferation of endothelial cells, especially in the blood-vessels and pulp spaces, and the formation of venous thrombi.

In rare cases the softened spleen ruptures, with an extravasation of blood into the peritoneal cavity. There may be infarctions of the spleen, which sometimes soften and may apparently lead to peritonitis.

The Liver.—The liver may present no apparent lesion. It is, however, frequently large, pale, and flabby, and in this condition the liver cells may be the seat of simple albuminous degeneration.

Less frequently there are present in the liver very small, soft, grayish nodules (Fig. 150). These focal lesions are sometimes too small to be distinguished by the naked eye. They may be situated about the branches of the portal vein or within the lobule. Some of these nodules consist of masses of small spheroidal cells, which may form a diffuse infiltration along the small veins. Mallory distinguishes two distinct varieties of these focal lesions: one formed in the lymph-spaces and -vessels in the capsule of Glisson by a proliferation of the endothelium (Fig. 151); the other due to obstruction of liver capillaries, in part by the proliferation of endothelium on the spot, in part by emboli of endothelial-cell origin, which are derived through the portal circulation from the vessels of the spleen and intestine. Necrotic changes may develop in and about these focal cell accumulations.

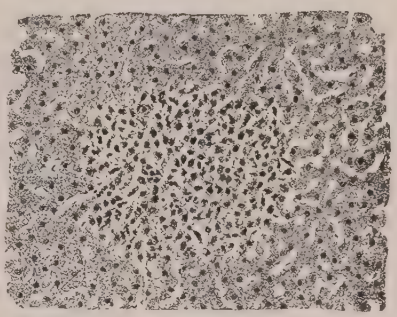


Fig. 150.—Focal Area of Endothelial-cell Proliferation in the Liver in Typhoid Fever.

Simple focal necroses of the liver and of other viscera, due to the action of toxic substances in the body fluids, may occur in typhoid fever as in many other infectious diseases.[1]

[1] For fuller details of studies on these focal lesions in typhoid and other infectious diseases, consult *Mallory*, Jour. Exper. Med., 1898, iii, 611; *Reed*, Johns Hopkins Hosp. Rep., 1895, v, 379; and *Flexner*, ibid., 1897, vi, 259.

While small foci of cell proliferation may be present in the *kidneys* as well as in other viscera, their occurrence is neither so frequent nor so characteristic as in the liver.

In typhoid fever as in other infectious diseases toxemia may be manifested by disturbances in the circulatory, respiratory, and heat-regulating mechanism, and in general metabolism, as well as by manifest lesions, such as albuminous or other degeneration of parenchyma cells throughout the body, and alterations leading to leucocytosis.

Secondary Lesions.

In addition to the more characteristic lesions of typhoid fever which we have described, there are several of secondary or complicating nature. These are of sufficiently frequent occurrence in the disease to require brief mention. They are in part due to the direct action of the typhoid bacillus or its soluble poisons; in part, however, they are brought about by secondary bacterial infections.[1]

The Digestive Organs.—In the *intestine* there may be gangrene, sometimes involving the tissues about the ulcers, sometimes apart from these. There may be croupous inflammation of the intestinal mucous membrane of either the large or small intestine. A slight peritonitis sometimes accompanies the intestinal lesion. A severe peritonitis is usually due to perforation, less frequently to ulcers which reach the serous coat, but do not perforate. When there is infiltration of the serous coat with the new cell growth, described above, peritonitis may be associated with a production of little gray nodules of the same character throughout the peritoneum. In-

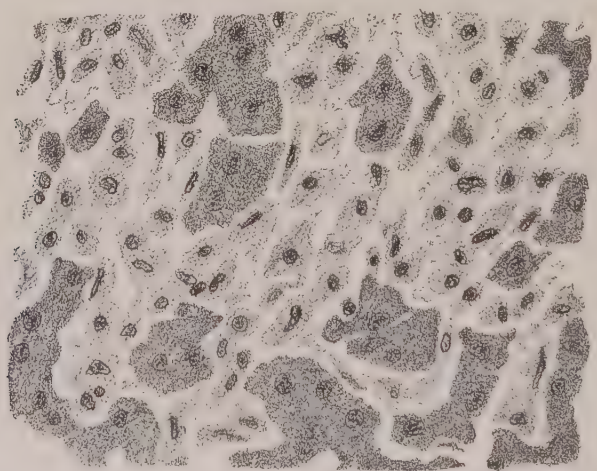


Fig. 151.—Hyperplasia of Endothelium in the Liver in Typhoid Fever. This cut shows a more highly magnified portion of the focal lesion in Fig. 150.

farctions of the spleen, inflammation of the ovaries, and perforation of the gall-bladder are sometimes the inciting factors in peritonitis.

Hemorrhage from the intestines may be slight and due to the inflammatory swelling and congestion of the mucous membrane; or it may be due to the ulceration of the follicles and opening of the blood-vessels, and is then often profuse.

There may be hyperplasia of the tonsils and of the lymphoid tissue at the base of the tongue. Gangrenous ulcers of the sides and floor of the mouth may be present. Catarrhal and croupous inflammation of the pharynx may be associated with super-

[1] For bibliography of the extra-intestinal lesions induced by the typhoid bacillus, see *Howard*, Philadelphia Monthly Med. Jour., 1899, i, 402.

ficial or deep ulceration. Inflammation of the *parotid* leading to suppuration is not infrequent. The *submaxillary gland* may be similarly affected. Enlargement and induration of the *salivary glands* and of the *pancreas* in typhoid fever have been described and are believed to be due to hyperplasia of the gland cells with accumulation of their secretion. This may be followed by degeneration.

The Circulatory Organs.—The *heart* in many cases is the seat of albuminous, fatty, or hyaline degeneration, or of pigmentation. Myocarditis, endocarditis, and pericarditis are of occasional occurrence. Thrombi may form upon the valves or in the heart cavities, and detached fragments of these may be lodged as emboli in various parts of the body. The *arteries* may be the seat of acute inflammation. If this involve the intima, an occluding thrombus may be formed which may lead to gangrene of the part supplied by the vessel. Thrombosis of the *veins* is common, and especially frequent in the femoral vein late in the disease.[1]

The Respiratory Organs.—The *larynx* is frequently the seat of catarrhal inflammation, with or without superficial erosions. Less frequently there is croupous inflammation, followed in some cases by destructive ulceration; edema of the glottis occasionally occurs.

The Lungs.—Catarrhal inflammation of the large bronchi is very common. Bronchopneumonia occurs in two forms. There may be a severe inflammation of most of the bronchi of both lungs, with cellular infiltration of the walls of the bronchi and zones of peribronchitic pneumonia; or there may be an intense general bronchitis, with lobules of the lung corresponding to obstructed bronchi, either collapsed or inflamed, or both.

From the long-continued recumbent position of the patients, the posterior portions of the lungs become congested, dense, and unaerated. Sometimes, in addition to this, irregular portions of the lungs become hepatized. Less frequently there is acute lobar pneumonia. Infarctions are not uncommon, and gangrene occasionally occurs, either associated with lobular pneumonia or with infarctions, or as an independent condition. Fibrinous pleurisy and empyema are not infrequent.[2]

The Genitourinary Organs.—The *kidneys* are occasionally the seat of an acute inflammation. Catarrhal and croupous and nodular inflammation of the *bladder* may occur. Hemorrhage and gangrenous inflammation in the *ovaries* have been recorded; the uterus may be involved. *Orchitis* and *epididymitis* may develop during convalescence.[3]

The Nervous System.—In addition to chromatolytic changes in the ganglion cells, which are common to many infectious diseases,[4] there may be thrombosis of the venous sinuses and obliterating endarteritis. Acute meningitis is rare.[5] Degeneration and inflammation of the peripheral nerves may occur.

Suppurative inflammation may occur in almost any part of the body in typhoid fever. This may be in the form of boils or of deep abscesses. Postpharyngeal suppuration is often one of the most serious of these complications. Posttyphoid bone lesions are often important.[6]

Septicemic Forms of Typhoid Fever Without Characteristic Local Lesions.

Typhoid fever may occur without the characteristic intestinal and associated lesions. In this septicemic type of the disease there may be no demonstrable lesions other than those which are due to the toxemia.[7]

[1] See an analysis of forty-two cases of venous thrombosis in typhoid fever, *Thayer*, Tr. Assn. Am. Phys., 1904, ix, 164.

[2] For pulmonary complications, see *Robinson*, Proc. Path. Soc., Philadelphia, 1905, viii, 141.

[3] See *Kinnicutt*, Tr. Assn. Amer. Phys., 1901, xvi, 145.

[4] For a study of ganglion cells in cases of typhoid fever, see *Nichols, J. L.*, Jour. Exper. Med., 1899, iv, 189 (bibl.). See also *Ewing, J.*, Arch. Neurol. and Psychopath., 1898, i, 263.

[5] For study of typhoid meningitis, see *Cole, R.*, Johns Hopkins Hosp. Rep., 1904, xii, 379.

[6] *Parsons*, Johns Hopkins Hosp. Rep., 1895, v, 417. For a study of bone-marrow in typhoid and other infections, see *Longcope*, Proc. Path. Soc., Philadelphia, 1905, viii, 49.

[7] Consult in this connection, for cases and bibl., *Chiari*, Ztschr. f. Heilk., 1897, xviii, 5; and *Ophüls*, New York Med. Jour., 1900, lxxi, 728 (bibl.).

On the other hand, inflammatory processes in the viscera—lungs, kidney, spleen, etc.—may be dependent on the presence of the typhoid bacillus. The lesions in such cases are not, so far as we yet know, characteristic, and the post-mortem diagnosis depends largely upon the identification of the bacillus.[1]

Distribution of the Typhoid Bacillus in the Body in Typhoid Fever.

In the early stages of the disease the bacillus may be found in the lymphatic structures of the intestines and in the mesenteric lymph-nodes and the spleen. It may be present in lesions involving the bone-marrow, kidney, liver, lungs, pleura, uterus, and testicle, and in the rose spots of the skin,[2] as well as in the blood, where it may be found in a large proportion of cases.[3] In at least 20 per cent. of cases in the third and fourth weeks, typhoid bacilli have been found in the urine, usually accompanied by albumin, and in the bile, and they may persist in both of these and in the feces long after the establishment of convalescence.[4] They may be found, though not in such abundance as was formerly assumed, in the intestinal contents after the disease has become well established.[5] Their abundance here appears to depend somewhat upon the degree of intestinal ulceration. In the viscera they are apt to occur in larger and smaller masses or clusters (see Fig. 152). The typhoid bacillus may be transmitted through the placenta to the fetus.

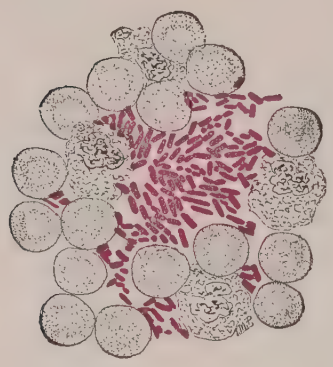


Fig. 152.—Cluster of Typhoid Bacilli in the Spleen.

Typhoid bacilli may be present alone or in association with other germs in the foci of suppuration which so frequently complicate typhoid fever, also in the exudate in inflammations of the serous membranes and in the endocardial vegetations.[6]

Mixed Infection.—Some of the inflammatory complications which occur in typhoid fever are due to the growth of the bacillus in unusual places in the body; but many of them are due to a secondary infection with other germs, notably with the pyogenic cocci,[7] and also with the colon bacillus and the pneumococcus.[8]

[1] For summary of studies on the typhoid bacillus and typhoid fever, with bibl., consult *Dunbar L. O.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, i, 605; *Kutscher*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, iii, 717; and *Gay*, Typhoid Fever, New York, 1918.

[2] See *Pratt*, Jour. Boston Soc. Med. Sc., 1899, iii, 170.

[3] See *Coleman* and *Buxton*, Jour. Med. Research, 1909, N. S. xvi, 83.

[4] *Gwyn*, Bull. Johns Hopkins Hosp., 1899, x, 109; also *Curschmann*, on typhoid cystitis, München med. Wchnschr., 1900, xlvii, 1449

[5] *Hiss*, Med. News, 1901, lxxviii, 728.

[6] See *Flexner*, Jour. Path. and Bacteriol., 1895, iii, 202, and Johns Hopkins Hosp. Rep., 1897, v, 343; also *Macé*, Traité de Bacteriologie, 1901.

[7] For full consideration of the pyogenic powers of the typhoid bacillus, consult *Dmochowski* and *Janowski*, Zieglers Beitr., 1895, xvii, 221.

[8] *Keen*, Surgical Complications of Typhoid Fever, Philadelphia, 1898; *Hare* and *Beardsley*, Medical Complications of Typhoid Fever, Philadelphia, 1909.

Modes of Infection with the Typhoid Bacillus.

Infection with the typhoid bacillus seems usually to occur through the gastrointestinal canal. In very many cases the bacilli are conveyed by means of food, especially of milk and drinking-water, which have been polluted with the excretions—feces and urine—of persons suffering or convalescent from the disease. Many serious epidemics of typhoid fever have been traced to pollutions of milk and drinking-water from such sources.[1]

Oysters which have been taken from grossly polluted waters, as near sewer openings, have been the means of conveying the germs.[2] There is abundant evidence that flies convey the infectious material from undisinfected discharges.[3]

In milk the typhoid bacillus not only remains alive for long periods, but undergoes active multiplication. It may remain long alive in water but in steadily diminishing numbers.[4] In the soil and when dried it may remain alive for months. Frozen in ice it has been found alive after more than three months, but here also the bacilli are gradually reduced in number and finally die out. It is readily killed by exposure to strong sunlight.

Typhoid Carriers.—While the presence of typhoid bacilli in the bile and gall-bladder, and even very exceptionally in the blood of healthy persons, has been recognized for some time, it is only comparatively recently that it has become definitely and widely known that the typhoid bacilli may remain in the gall-bladder for many years. Park states that from 1 to 5 per cent. of typhoid convalescents may continue to pass typhoid bacilli for years.[5] In these cases the bacilli may be continually discharged in the feces, or in some instances in the urine. Such persons are called "typhoid carriers" and if they are of uncleanly habits or are engaged in handling foods as cooks, milkmen, etc., may lead to the infection of many persons. Attempts have been made to remove the source of infection by excision of the gall-bladder, but this procedure is justified only when gall-stones are present. Vaccines also have been employed with only fairly satisfactory results.

Immunity and Preventive Inoculations.

One attack of typhoid successfully overcome gives a certain measure of protection, though this is not absolute, against another. Animal experiments have shown that it is possible to secure immunity against deadly doses of typhoid bacilli, either by the

[1] *Anderson, J. F.*, Med. Rec., 1908, lxxiv, 909; also *Vaughan*, Jour. Am. Med. Assn., 1902, xxxviii 979. For résumé with bibl. of viability of typhoid bacillus under various conditions, see *Wheeler*, Jour. Med. Research, 1906, N. S. x, 269.

[2] *Freeman, R. G.*, Albany Med. Ann., 1897, xviii, 135 (bibl.); *Brooks, P. B.*, Jour. Am. Med. Assn. 1916, lxvi, 1445.

[3] *Graham-Smith*, Flies in Relation to Disease, Cambridge, 1913; *Howard*, U. S. Dept. Agriculture Bureau of Entomology, Bull. 78, 1909; and *Ficker*, Arch. f. Hyg., 1903, xlvi, 274; also report on typhoid fever in U. S. Military Camps during Spanish War of 1898, by *Reed, Vaughan*, and *Shakespeare*, 1900.

[4] See *Jordan, Russell*, and *Zeit*, Jour. Infect. Dis., 1904, i, 641; also *Russell* and *Fuller*, ibid., Suppl. No. 2, 1906, p. 40.

[5] For typhoid carriers, see *Park* and *Williams*, Pathogenic Microorganisms, 6th ed., New York 1917, p. 339; *Ledingham*, Carrier Problem in Infectious Diseases, 1912 (bibl.); *Chapin*, Sources and Modes of Infection, New York, 1912; *Stone*, Am. Jour. Med. Sc., 1912, cxliii, 544; and *Gay*, Typhoid Fever, New York, 1918.

inoculation in increasing amounts with sensitized living typhoid-bacillus cultures, or by the injection of suspensions of the bodies of the dead bacilli.

Preventive inoculations have been practised on a large scale in man by the method of Haffkine with very favorable results. In this method emulsions of the bacillus are killed by heating to 53° C. for an hour; tricresol is added to insure sterility; and a known number of organisms are injected intramuscularly. A number of different types of vaccine have been employed, even live bacilli.[1]

There is a slight and temporary local and general reaction which may be manifested with diminished intensity on the subsequent injections made after a few days' interval.

By comparing the records of thousands of persons inoculated with dead typhoid bacilli, with an equal number not inoculated and exposed to the same conditions, it has been found that practically no cases of typhoid fever occurred in the inoculated group, and that in the few instances in which the disease was present it was of a much less severe type than that which occurred in the uninoculated group.

In the United States this method of preventive inoculation has been practised on a large scale in the army with extraordinarily favorable results.[2]

Agglutinins, Precipitins, and Opsonins.

We have seen in an earlier section of this book (page 212) that in the adaptation of a living body to certain alien organic substances, among which are bacteria and their toxins, the serum of the adapted—or in the case of microorganisms, of the immunized—individual may contain substances which are *agglutinative* for the particular species of microorganism involved. By the use of this phenomenon of agglutination, a method of clinical diagnosis of considerable value has been devised and much employed especially in typhoid fever.[3]

Specific *precipitins* also are formed in the adaptation of the organism to the typhoid bacillus.[4]

Opsonins are formed in animals artificially immunized to the typhoid bacillus and also in man during typhoid fever. But determination of the opsonic index is difficult owing to the rapid lysis of the bacilli in the serum and in the phagocytes.

The Typhoid and Colon Bacillus.

Much difficulty has been encountered in separating the typhoid bacillus from various forms of the colon bacillus when they occur together, as may be the case in contaminated water or in the dejecta of persons suffering from typhoid fever. The more actively growing colon organisms obscure the few small typhoid colonies which may be present. A large number of special plating media have been devised, many of them employing the different color reactions induced in aniline dyes by the growth of the two types of organism.

Hiss demonstrated that by a slight modification of the common methods the growth of each form is quite characteristic, so much so that pure cultures may be made from the mixed plates without difficulty.[5] When once the two forms are separated, distinguishing characters are readily demonstrable.[6]

Method of Staining the Typhoid Bacillus.

The bacilli from artificial cultures stain readily with the ordinary aniline dyes, such as fuchsin and methylene blue. In sections, however, they do not stain so readily.

[1] See for a review of this method, *Wright*, Brit. Med. Jour., 1904, ii, 1343.

[2] See *Russell*, Harvey Lectures, Philadelphia, 1912–1913, also Am. Jour. Med. Sc., 1913, cxlvi, 803. For a study of the efficiency of the various types of vaccines, see *Sawyer*, Jour. Am. Med. Assn., 1915, lxv, 1413.

[3] For further details of agglutination we refer to the works on clinical pathology, and for bibliography to *Craw*, Jour. Hyg., 1905, v, 113.

[4] *Norris*, Jour. Infect. Dis., 1904, i, 463.

[5] *Hiss*, Jour. Exper. Med., 1897, ii, 677; Jour. Med. Research, 1902, N. S. iii, 148; also *Hiss* and *Russell*, Med. News, 1903, lxxxii, 289. See also the standard bacteriological text-books.

[6] For a study of agglutinative reactions of the colon-typhoid group, see *Bruns* and *Kayser*, Ztschr. f. Hyg. u. Infectionskrankh., 1903, xliii, 401.

They are decolorized by Gram; and in sections, may be stained by *Ziehl's solution*. Stain for half an hour, decolorize in alcohol, clear in oil of cedar, mount in balsam. The decolorization in alcohol should be carefully done to avoid the removal of too much color. Flexner recommends *Loeffler's methylene-blue solution* for two hours; then acetic-acid solution 1:1,000 for several minutes; dehydrate in absolute alcohol; clear and differentiate in oil of cloves; mount in balsam. The aim in both of these methods is to leave the cell nuclei faintly colored, but not so much so as to conceal the clusters of more deeply stained bacilli.

PARATYPHOID.

The study of a number of cases of disease resembling typhoid fever has revealed a class of organisms of the colon-typhoid group which are pathogenic for man and of which three types, separable by their cultural and agglutination peculiarities, have been recognized. The organism most frequently found is distinguished as paratyphoid B; this incites a disease closely resembling typhoid fever, but running usually a somewhat shorter clinical course. In another group of infections, usually following the eating of spoiled food, the symptoms are those of an acute gastroenteritis; while in still a third type the symptoms more closely resemble those of cholera. In all cases the bacilli are usually found in the blood. The agglutinative reactions of these organisms show to a high degree the so-called group agglutinins, the organisms of groups other than that causing the infection being agglutinated by the patient's serum in ordinary dilutions, and the specific agglutination for the invading organism appearing only when very high dilutions are used.

The disease is not very common in the United States except in the military camps. In these situations it has not infrequently occurred in persons who have been vaccinated against typhoid fever, and in consequence at the present time the soldiers are vaccinated also against both paratyphoid A and paratyphoid B organisms. The protection offered does not seem to be as lasting or as complete as that conferred by typhoid vaccination.

As the organisms do not form a distinct group and the clinical symptoms of the disease differ so greatly, it is to be expected that the pathological findings are not wholly characteristic. The lesions are frequently very small in extent, but occasionally there is swelling and ulceration of the Peyer's patches, enlargement of the spleen, Zenker's degeneration of muscle fibers, and other changes which are usually seen in cases of typhoid fever.[1]

DYSENTERY.

This form of infectious colitis is regularly associated with and doubtless incited by bacilli of the colon-typhoid group. One of these is the

[1] *Schottmüller*, Deutsch. med. Wchnschr., 1900, xxvi, 511; *Wells* and *Scott*, Jour. Infect. Dis., 1904, i, 72; *Saltykow*, Virchows Arch., 1913, ccxi, 467; *Uhlenhuth* and *Hübener*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, iii, 1005 (bibl.); and *Gay*, Typhoid Fever, New York, 1918. For bacteriological studies of paratyphoid bacilli and methods of differentiating organisms of the paratyphoid-enteritidis group, see *Proescher* and *Reddy*, Jour. Am. Med. Assn., 1909, lii, 470, Arch. Int. Med., 1910, v, 263 (bibl.); and *Krumwiede, Pratt*, and *Kohn*, Jour. Med. Research, 1916, N. S. xxix, 355; 1916–17, N. S. xxx, 55, 357; 1917, N. S. xxxi, 509; 1918, N. S. xxxiii, 89.

organism originally described by Shiga[1] which has long carried his name; in addition, three other types have been described,[2] which are separated by their fermentation reactions. The organisms are found also in cases of summer diarrhea among children. The infection is often severe, with a high degree of intoxication.

The lesions of the disease vary from a slight catarrhal inflammation to a diffuse pseudomembranous or gangrenous inflammation of the wall of the gut (see page 780).[3]

The disease is transmitted probably through contamination of food and water. Healthy and convalescent carriers have been found, even up to 50 per cent. of those who suffer from an attack of the disease. Good therapeutic results have been reported from the use of polyvalent sera. The diagnosis of the type can as a rule be made by agglutination reactions, but as these are often not very strong it is sometimes necessary to fall back upon cultural methods.[4]

ASIATIC CHOLERA.

Asiatic cholera is a disease incited by the growth and proliferation in the intestines of a slightly curved or spiral-shaped bacterium, which is called the cholera spirillum—*Spirillum choleræ asiaticæ* (*Vibrio choleræ asiaticæ*). This organism in the early and active stages of the disease may be present in enormous numbers in the contents of the small intestine, often penetrating the mucosa. It is usually confined to this situation. Its deleterious effects upon the body appear to be largely due to the production of toxic substances, which on absorption, in addition to serious intestinal irritation or lesion, may incite those systemic disturbances which characterize profound toxemia.

In addition to the action of the toxins the extraordinary desiccation of the body due to the enormous loss of fluid from the bowel and made evident by the polycythemia which exists, seems to play a very important part in the symptomatology and course of the disease. The passage of large quantities of alkaline fluid also increases the alkali deficit of the body with the production of an acidosis. Very successful therapeutic results have been reported from the use of intravenous infusions of large quantities of normal saline and of 4 per cent. sodium bicarbonate solutions. The first replaces the fluid lost, the second neutralizes any excess of acid. The benefits of the alkaline treatment have been especially evident in persons approaching the uremic stage in cholera.[5]

Lesions of Asiatic Cholera.

In some cases of cholera there are no definite changes to be found after death, and in no case are the lesions distinctive of this disease.

[1] *Shiga*, Centralbl. f. Bakteriol., Orig. I, 1898, xxiii, 599; xxiv, 817, 870, 913; Deutsch. med. Wchnschr., 1901, xxvii, 741, 765, 783.

[2] *Flexner*, Bull. Johns Hopkins Hosp., 1900, xi, 39; *Hiss* and *Russell*, Med. News, 1903, lxxxii, 289; *Strong* and *Musgrave*, Report, Surgeon General, U. S. Army, Washington, 1900.

[3] *Lentz, O.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, iii, 899 (bibl.).

[4] *Hiss*, Jour. Med. Research, 1904–05, N. S. viii, 1.

[5] *Rogers*, Lancet, 1917, ii, 745: see also *Sellards*, The Principles of Acidosis, Cambridge, 1917, p. 54.

If death occur during the invasion of the disease or in the stage of collapse, the appearances in the more pronounced cases may be summarized as follows:

The body may remain warm for some time, and the temperature may rise for a short time after death. The rigor mortis usually begins early and lasts for an exceptionally long time. The muscles sometimes exhibit a peculiar spasmodic twitching before the rigor mortis sets in, especially the muscles of the hand and arm.

The skin is of a dusky gray color; the lips, eyelids, fingers, and toes are of a livid purple. The ends of the fingers are shrivelled, and the cheeks and eyes sunken.

The Brain.—The sinuses of the dura mater are filled with dark, thick blood. The pia mater may be normal, or edematous, or ecchymotic, or infiltrated with fibrin. The brain is usually normal, but may be dry and firmer than usual.

The lungs are retracted and anemic, the pleura may be dry or coated with fibrin. **The heart** is normal. **The peritoneum** may be dry or coated with a layer of fibrin.

The stomach is usually unchanged, but may be the seat of catarrhal inflammation. In the **small intestine** there may be ecchymoses in the mucous membrane; the mucous membrane may be soft and edematous; there may be general congestion, or the congestion may be confined to the peripheries of the solitary and agminated nodules, and these nodules may be swollen; or there may be croupous inflammation and superficial necrosis. All these changes are usually most marked at the lower end of the small intestine. There is apt to be post-mortem desquamation of the epithelium. The characteristic rice-water fluid may be found in the intestines after death, or, instead of this, dark-colored, bloody fluid. **The large intestine** is usually normal, but in some epidemics croupous inflammation occurs in a considerable number of cases.

The spleen may be soft, and normal in size or enlarged. **The liver** may show small areas of granular or fatty or hyaline degeneration.

The kidneys are often increased in size, with white and thickened cortex and congested pyramids. The epithelium of the cortical tubes may contain coarse granules and fat globules, or be necrotic. The tubes may contain casts and disintegrated epithelium. **The uterus** and **ovaries** may be congested and contain extravasated blood.

If the patient does not die until the stage of reaction, the body does not present the same collapsed appearance, and there are often inflammatory changes in different parts of the body, especially in the larynx, the lungs, the stomach, and the intestines.

Characters of the Cholera Spirillum.

The cholera spirillum, which was discovered by Koch in 1885, is a curved rod with rounded ends, from 0.8 to 2.0 μ long, asporogenous, aerobic, and motile. When growing under suitable conditions these rods are apt to cling together by their ends, forming S-shaped structures or spirals, often of considerable length (Fig. 153). The organism stains readily and grows abundantly on the ordinary culture media. The life period is short and various degenerative "involution" forms are apt to be present in old cultures.

It grows best at about blood heat, growth ceasing at about 16° C., but it may survive a reduction of the temperature to –10° C. It is quickly killed by drying or by the temperature of boiling water. Acids are inimical to its growth. It may retain its vitality for a considerable time in water. On moist surfaces, such as damp linen, earth, or vegetables, or in milk, it may rapidly proliferate.

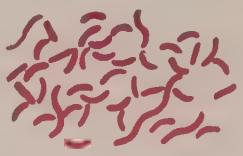


Fig. 153.—Spirillum Choleræ Asiaticæ. From a culture.

Pathogenesis.—The results of animal experiments with the cholera germ are not in themselves decisive in determining its relationship to this disease, since animals do not react in its presence as man does. However, the constant occurrence of this organism in Asiatic cholera, its absence from the body under other conditions, and the accidental laboratory infections which have several times occurred in men handling pure cultures of the germ, leave no doubt as to its significance as the excitant of this disease.

Bacterial Diagnosis.—It is often of the highest importance to determine, at the earliest possible moment, whether or not a suspected case be one of Asiatic cholera or some other form of acute intestinal disorder, so that in the former case the proper measures may be instituted to prevent the spread of the disease. The characters which are developed in cultures of the cholera bacillus enable an expert bacteriologist to distinguish this organism from all other known forms. But the scope of this work does not permit a detailed description of the cultural peculiarities of the germ; and the responsibility of such determinations should not be assumed without adequate preliminary laboratory experience. By taking together the morphological and biological characters, it is possible, usually on the second or third day, to determine whether the intestinal contents in a suspected case do or do not contain the bacillus of Asiatic cholera.[1]

Communicability.—Through milk or water or other uncooked food contaminated with the dejections of those suffering from Asiatic cholera, epidemics are lighted up and maintained. After drying, there appears to be relatively little risk from cholera discharges. Individual susceptibility plays an important rôle in this as in many other infectious diseases. For during cholera epidemics the spirillum has been found in many instances in the stools of apparently healthy persons. Such "cholera carriers" seriously complicate the problems of public sanitation and quarantine. The elements of susceptibility to Asiatic cholera are not yet understood, though it is commonly assumed that dietetic indiscretions and gastrointestinal disorders may be significant factors in the acquired disposition to the disease.

A certain degree of temporary immunity is acquired through recovery from the disease.

Toxic Products and Preventive Inoculation.

Toxic Products.—The toxic substances formed by the cholera spirillum are apparently set free to some extent in soluble form, but are largely such as are stored in the bacterial cell itself—*endotoxins*.

Pfeiffer has shown that the spirillum of Asiatic cholera, put into the peritoneal cavity of an artificially immunized guinea-pig, is quickly immobilized, swells and becomes granular, and soon disappears. A similar effect can be secured in tubes by a mixture of the immune serum

[1] For characters of the cholera organism, methods of diagnosis, etc., see *Kolle* and *Schürmann*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 1.

and fresh serum to which the spirilla are added. This lytic effect of the immune serum upon the bacteria may be used as a test of the specific character of a suspected spirillum; and, on the other hand, with a definitely known spirillum the lytic action of the serum in a suspected case of disease may be valuable as a diagnostic aid.

This bacteriolytic action of specific sera is not peculiar to the so-called anti-cholera serum, but has been observed in other cases—for example, in typhoid serum with the typhoid bacillus. Its nature and its bearing on immunity have been considered in an earlier section of this book (page 202).

Agglutinative substances which may be of value in diagnosis, are also developed in Asiatic cholera.

Preventive Inoculation.—A large amount of work has been done looking toward artificial immunization of man against Asiatic cholera in the East, and preventive inoculation practised by the method of Haffkine appears to have given encouraging results. This method consists in the subcutaneous injection of cultures of the cholera bacillus; first, those whose virulence has been diminished, and then, those in which the virulence has been exalted by artificial means.

But the Haffkine preventive inoculation with living cultures has been in a large measure superseded by the injection of a small amount of a fresh agar culture killed by heat. The dose is repeated after a few days. There is moderate local and general reaction to the injections. The serum of persons thus twice injected, after two or three weeks, may show the development of bactericidal substances exceeding in efficiency those present during convalescence from the disease. Such an active, artificial immunity may last for many months. The practical result of this form of preventive inoculation on a large scale in Japan has been a considerable reduction in the proportion of cases in the protected groups, as compared with others similarly exposed, as well as a reduction in the mortality of those who in spite of the protective attempt contracted the disease.[1]

Other Spirilla Resembling the Cholera Spirillum.

There are several fairly distinct forms of spirilla, some of which appear to be related to the cholera organism, which have been occasionally found in various situations. One of these is the so-called *Vibrio proteus* or spirillum of Finkler and Prior. This organism was found by these observers in the dejecta of persons suffering from cholera nostras, shortly after the discovery by Koch of the cholera spirillum, which at first it was thought closely to resemble. The cultural characters, however, abundantly suffice to differentiate the organisms. The Vibrio proteus is slightly pathogenic for certain lower animals, but not for man.

Several forms of spirilla of somewhat similar general characters have been found in various situations; thus in cheese, by Denecke, *S. tyrogenum;* in a chicken epidemic and in sewage, by Gamaleia and by Pfuhl, *Vibrio metschnikovi;* in the dejecta during a cholera epidemic at Massawah, *Vibrio massawah*, etc.

[1] For a study of protective inoculations against Asiatic cholera, see *Hetsch*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 110.

TUBERCULOSIS.[1]

Tuberculosis is an infectious disease characterized by inflammatory and necrotic processes in the body and incited by the presence and growth of the Bacillus tuberculosis (tubercle bacillus). The most distinctive morphological feature of tuberculosis is the development under the influence of the tubercle bacillus of larger and smaller, gray or white or yellow, firm or friable masses of tissue called *tubercles*.

The effect on the body-cells of the presence and growth of the tubercle bacillus varies considerably, depending upon the number and virulence of the germs present, the character of the tissue in which they lodge, and the vulnerability of the individual. In general, it may be said that tubercle bacilli may stimulate the connective-tissue cells in their vicinity to proliferation; or they may excite emigration of leucocytes from blood-vessels and lead to the production of other exudates; or they may cause death of tissue. Thus the phases of inflammation which are excited by the tubercle bacillus are *productive*, *exudative*, and *necrotic*. The tubercle bacillus may incite these changes separately or simultaneously, in the sequence just indicated or in some other; and now one, now another of them may preponderate.

Morphology of the Lesions of Tuberculosis

Tuberculosis manifests itself most often in the form of an inflammation affecting some one part of the body, as the lungs and bronchial lymph-nodes (the parts most frequently involved in adults), the gastro-intestinal tract, or the skin—"*localized tuberculosis*." In a considerable proportion of cases the local lesions induced by the tubercle bacillus are in the form of circumscribed nodules or masses of new-formed cells or tissue which are called *tubercles*, or, if small, *miliary tubercles*.[2]

Such a localized tuberculosis may retain throughout the characters of a local inflammation, or it may be accompanied by the clinical evidences of systemic infection. It may give rise through metastasis to the successive development of tuberculous inflammations in other parts of the body, or to a sudden development of small foci of tuberculous inflammation in many parts of the body at the same time—*general miliary tuberculosis*.

A general infection may occur by the diffusion through the body of bacilli derived from a local tuberculosis, such as tuberculous phlebitis

[1] Some authors are disposed to class together, under the name *Infectious Granuloma*, lesions induced by microorganisms, certain phases of which are characterized by a localized, usually slow, nodular growth tending to necrosis. The more important of these are tuberculous, leprous, syphilitic, and actinomycotic. It may be doubted whether it is wise to group together, under a name suggesting tumor relationships which do not exist, lesions of such diverse origin and clearly of infectious character.

[2] The term *miliary tubercle*, which arose from the coincidence in size between small foci of tuberculous inflammation and some forms of millet seed, is now very liberally applied to tubercles which are very much larger as well as to those which are very much smaller than millet seeds. It is convenient to designate a small mass of new tissue formed under the influence of the tubercle bacillus, whatever its minute structure, as a *tubercle granulum* (see Fig. 155). Very frequently two or more tubercle granula are joined together by a more diffuse formation of tubercle tissue to form larger or smaller miliary tubercles—*conglomerate tubercles* (see Fig. 156).

or arteritis, or tuberculous inflammation of the thoracic duct (Fig. 154), or from the breaking into a vessel of a tuberculous lymph-node. It is probably seldom that tubercle bacilli enter the blood-channels at one time in sufficient quantity to account for the enormous numbers of tubercles which are sometimes found in acute general miliary tuberculosis; but it is not unlikely that, from the newly formed tubercles which develop in the walls of the smaller blood-vessels, new distributions of bacilli may take

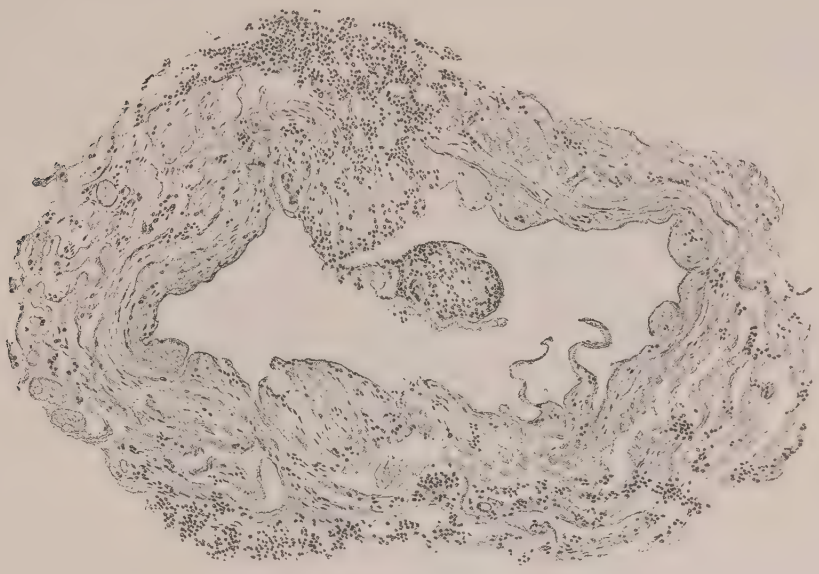


FIG. 154.—TUBERCULOSIS OF THE THORACIC DUCT.
From a case of generalized miliary tuberculosis.

place from time to time as the tubercles mature. This probability is sustained by the frequent occurrence of miliary tubercles on the intima of the small arteries in the lung for example, as well as by the evidence of differences in age of the individual tubercles in generalized miliary tuberculosis.[1]

Diffuse Tuberculosis.—In many cases, however, the lesion is not focal or circumscribed but diffuse, and more or less widely infiltrates or replaces the tissues involved. This is called *diffuse tuberculous inflammation*.

Miliary Tubercles.—Miliary tubercles are small nodules of irregular shapes (Plates VI, VIII, and IX), the smallest hardly visible to the

[1] It is well, in the endeavor to understand the occurrence of general miliary tuberculosis or of the less striking instances of distribution of the bacilli, to remember that two varying factors are constantly active and significant: first, the virulence of the bacilli, which may be slight or extreme; and, second, the vulnerability of the infected individual—*i.e.*, his "predisposition"—which also may be slight or extreme. Thus the distribution of bacilli, be these few or many, from an infective focus, may be in different individuals or at different times in the same individual of quite different significance. For a résumé of the discussion as to the sudden or gradual origin of miliary tubercles see *Ribbert, H.*, Deutsch. med. Wchnschr., 1906, xxxii, 5. *Silbergleit, H.* (Virchows Arch., 1905, clxxix, 283), was able by careful searching to find a vascular tubercle, most frequently in the pulmonary veins, occasionally in the thoracic duct, aorta, and other vessels, in about 95 per cent. of the cases of miliary tuberculosis examined by him.

naked eye. The smaller tubercles are gray and translucent; the larger are usually, especially in the central parts, opaque and white or yellow on account of the necrosis which is apt to commence here.

In studying the reaction of the living tissues to the tubercle bacillus it should be always borne in mind that while, as a whole, the lesions produced are quite characteristic, there is still no one structural feature or combination of features of tubercles or tuberculous inflammation which is absolutely distinctive of the action of this bacillus. In doubtful cases the demonstration of the presence of the germ itself may be necessary for the establishment of the character of the lesion.[1] This is espe-

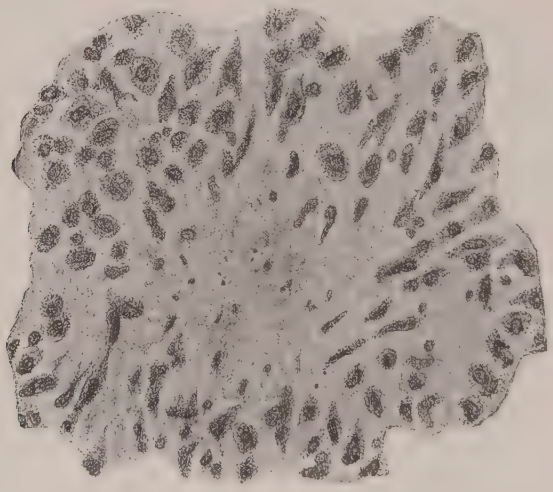


FIG. 155.—A SMALL MILIARY TUBERCLE.
This is growing in the liver and is composed mostly of new-formed polyhedral cells closely packed with little intercellular stroma. At the center, coagulation necrosis is commencing.

cially true in certain hypertrophic tuberculoses of the large intestine, and the procedure may be necessary also when the number of tubercle bacilli present is so small that a very slight and quite uncharacteristic reaction takes place.

Experimental studies in animals and in vitro show that when tubercle bacilli lodge and develop in the living body one of the early local effects is an active proliferation of the connective tissue, endothelial, lymphocytic, and reticular cells.[2] These become larger and polyhedral with conspicuous nuclei and form the "endothelioid" cell (Fig. 155).

A new reticulum or stroma may form hand-in-hand with the growth

[1] The term *tubercle tissue*, which is in common use, indicates a tissue formed under the influence of the tubercle bacillus rather than a tissue which is morphologically characteristic of tuberculosis in distinction from other forms of new tissue.

[2] The studies of *Wechsberg* indicate that the first effect of the tubercle bacillus upon living tissue is destructive so that the cell proliferation which follows is not due to a direct formative stimulus but this is contradicted by the *in vitro* studies of Maximow and others. See *Wechsberg, F.*, Zieglers Beitr., 1901, xxix, 203; also *Herxheimer, G.*, ibid., 1903, xxxiii, 363 (bibl.), *Herxheimer* and *Roth*, ibid., 1916, lxi, 1; *Maximow, A. A.*, Ann. d'Anatomie Pathologique, 1926, iii, 1.

of these new cells, or the old stroma may persist, adapting itself in form and arrangement to the new conditions.

Either after the connective-tissue cell proliferation or hand-in-hand with it, or preceding it, or altogether independently of it, emigration of leucocytes and extravasation of serum may take place from blood-vessels in the vicinity of the germs. During the more or less active cell proliferation which occurs under the influence of the tubercle bacillus, multinuclear cells—giant cells—may be formed (Fig. 156), either by persistent nuclear division in growing protoplasmic masses which do not divide into separate cells; or by the coalescence of the bodies of cells already formed. The former view of giant-cell formation is the one now most generally accepted.[1] Such cells may be produced with great rapid-

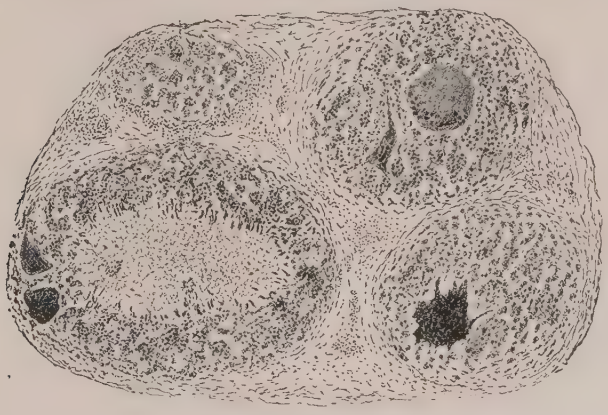


FIG. 156.—A MILIARY TUBERCLE WITH GIANT CELLS.
This tubercle is of the conglomerate type, made up of four granula, the larger one showing coagulation necrosis in the central portion. From the peritoneum.

ity, only thirty-six hours being required to form a miliary tubercle with a giant cell and surrounding epithelioid cells in experimental tuberculosis in the rabbit's liver. In this situation giant cells form from the so-called Kupffer cells lining the sinusoids. Within half an hour after the inoculation of tubercle bacilli, cellular reactions have been found in the interlobular capillaries. The polymorphonuclear leucocytes contain relatively few bacteria, but many of the Kupffer cells contain organisms. The polymorphonuclear leucocytes disappear at the end of half an hour and by this time mitotic figures are frequent in the Kupffer cells.

More or less new tissue with numerous small spheroidal mononuclear cells and little stroma may form in and about the tuberculous foci. Blood-vessels are not apt to develop under the influence of the tubercle bacillus Old blood-vessels are, on the other hand, usually obliterated as the new tissue forms.

Sooner or later under the influence of the tubercle bacillus, there is usually a damage of cell and tissue, which may lead to coagulation necrosis in the new-formed as well as in the old tissue of the infected

[1] *Herxheimer* and *Roth*, Zieglers Beitr., 1916, lxi, 1; *Evans*, *Bowman*, and *Winternitz*, Jour. Exper. Med., 1914, xix, 283.

region. This necrosis is more apt at first to manifest itself in the central portions of the tuberculous foci (Fig. 157) and may progress outward; the nuclei may become fragmented or disappear, or fail to stain in the usual way, the protoplasm may become more homogeneous; and cells and stroma may form at last an irregularly granular mass of tissue detritus which tends to disintegrate (coagulation necrosis, cheesy degeneration, caseation, see page 73), forming cavities or, if on free surfaces, ulcers.

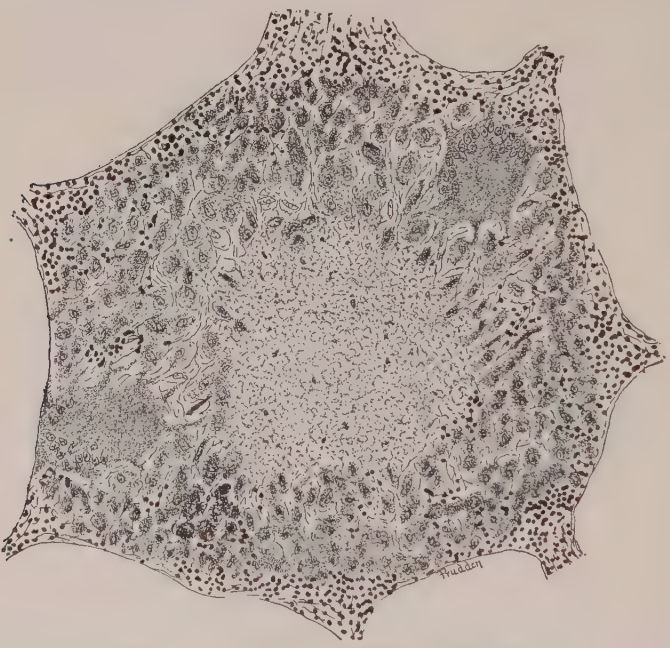


Fig. 157.—A Miliary Tubercle in the Lung.
Showing polyhedral cells, small spheroidal cells, and giant cells, with coagulation necrosis at the center.

As coagulation necrosis progresses, the tubercle masses lose the gray translucent appearance which in their early stages they are apt to present to the naked eye and become more opaque and of yellowish white appearance at the centers.

Finally dense fibrous tissue may form in and about foci of tuberculous inflammation, encapsulating or sometimes entirely replacing the more characteristic new-formed structures.[1] It is in this way—by the formation of connective tissue—that such repair as is possible after local tuberculous inflammation is brought about (Fig. 442, page 718).

Forms of Tubercles.—Before the discovery of the tubercle bacillus and while knowledge of the lesions of tuberculosis was largely limited to their morphology, it was natural that much stress should be laid upon the variety in structure which the nodular growths called tubercles

[1] Langhans' original paper contains interesting observations on the morphology of tubercles, and especially on the type of giant cell which bears his name. See, *Langhans, Th.*, Virchows Arch., 1868, xlii, 382.

present, and that elaborate classifications and groupings of tubercles were often deemed important.

With an exact knowledge of the excitant of the new growths and of the varying phases of their development in the body, the morphological peculiarities of tubercles are not now to be regarded as of such extreme significance, since they for the most part indicate simply variations in the local effect of a definite poison. These variations are due, as we have seen, to differences in the amount and intensity of the poison, to the degree of susceptibility of the individual, to the structure of the particular tissue or organ involved, and to the extent and variety of local complications caused by other agencies.

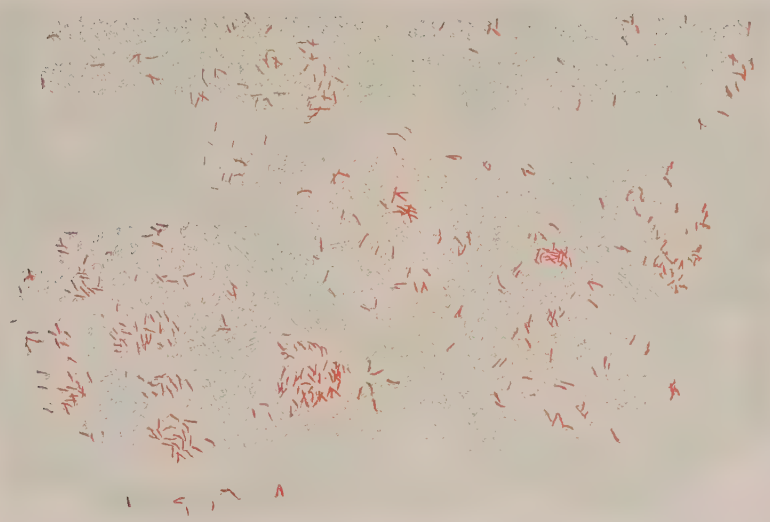


FIG. 158.—EXUDATIVE FORM OF TUBERCULOUS INFLAMMATION SHOWING TUBERCLE BACILLI. From the lung of a child. The size of the bacilli has been slightly exaggerated in the cut.

It is, however, usually convenient and sometimes important to recognize structural types in miliary tubercles. Thus they may be composed wholly of small spheroidal cells—"*lymphoid tubercles*," or of larger polyhedral cells—"*polyhedral-cell tubercles*," or of both forms of cells together and with or without a new-formed stroma; or of any of these combinations with giant cells. Then coagulation necrosis, which may occur in tubercles of any type; development of new dense connective tissue; association with various phases of simple exudative inflammation—all of these contribute to the variety in the structural types of miliary tubercles.

Diffuse Tuberculous Inflammation (Diffuse Tubercle).—1. If the infection with tubercle bacilli be extensive, or if step by step the bacilli are distributed in the tissues about the primary seat of infection, considerable amounts of tubercle tissue of one or other form may develop

and pass into the condition of coagulation necrosis, so that at length large necrotic masses, with a comparatively small amount of well-defined tubercle tissue, either diffuse or in the form of granula, may alone remain to indicate the character of old and slowly progressive local infection. This form of lesion is found in the large tuberculous masses in the brain, in the mucous membrane of the bronchi, in large flat masses on the serous membranes, and in the diffuse, cheesy infiltration of the lymph-nodes, kidneys, ureters, bladder, prostate, testicle, and uterus.

These large areas of tuberculous inflammation are apt to be white or yellow in the central and necrotic portions, which are sometimes dense, compact, and hard, sometimes soft and friable. These areas are not infrequently surrounded by an irregular gray zone of tubercle tissue or by a dense fibrous-tissue capsule.

2. In marked contrast with the phase of diffuse tuberculous inflammation just described, though often associated with it, is that in which the formation of inflammatory exudates is a prominent feature. This exudative form of tuberculous inflammation is best exemplified in the

Fig. 159.—Tubercle Bacilli in Sputum from a Case of Pulmonary Tuberculosis. Showing the bacilli stained with fuchsin, and pus cells stained for contrast with methylene blue.

lungs by some of the forms of acute phthisis (page 722). The tubercle bacillus is under certain conditions markedly pyogenic, and when it rapidly develops in the air spaces of the lungs or suddenly gains access to them in large quantities, pus, serum, fibrin, and exfoliated or proliferated epithelial cells may collect in and largely fill the air spaces, and then the whole new exudate and the old lung tissue may, over larger or smaller areas, rapidly undergo coagulation necrosis (Plates X and XII).

Thus in one phase of tuberculous inflammation the intensity and rapidity of the local poisoning by the bacillus do not permit of the formation of organized new tissue at all, but only of exudative products which are apt soon to become necrotic (Fig. 158). Less intense degrees of exudative inflammation are liable to develop in the vicinity of miliary tubercles anywhere in the body.

Characters of the Tubercle Bacillus.

The Bacillus tuberculosis is a long, slender bacterium varying in length from 2 to 4 μ (from one-quarter to one-half the diameter of a red blood-cell) and in breadth from 0.2 to 0.5 μ. It is frequently more or less curved, and the individual bacilli may cling together end to end, forming threads or chains. It may occur in branching forms.[1]

The bacillus (Fig. 159) is stained with difficulty by the aniline dyes (see below), and when stained often presents an irregular beaded or knobbed appearance, due to an unevenness in the coloring of the protoplasm, or to involution changes. It is immobile, and spores have not been demonstrated in it.

Fig. 160.—Culture of Tubercle Bacillus on Glycerin Agar.

From tuberculosis in man.

Fig. 161.—Culture of Tubercle Bacillus on Glycerin Agar.

From tuberculosis in bird.

At the temperature of the body it can be grown on many of the artificial culture media. The growth of the tubercle bacillus in cultures is very slow in comparison with that of most of the pathogenic microorganisms. After several weeks' growth it forms dry, scaly masses or thin, wrinkled pellicles on the surface of the media (Fig. 160 and 161). It requires a certain amount of oxygen for its growth, and thrives best in the dark.

[1] Branching forms of the tubercle bacillus have been frequently seen, and while their significance is not yet altogether clear, the tendency at this time is to separate this organism with the diphtheria bacillus and the so-called streptothrix or actinomyces forms into a group called higher bacteria. Whether, as many think, they are more closely allied to the moulds than to the bacteria, or whether, they should be considered in a class by themselves, is a problem still unsolved. For the present, we may wisely consider the tubercle bacillus as one of the bacteria.

For studies and bibliography on this subject consult *Schulze*, Ztschr. f. Hyg. u. Infectionskrankh, 1899, xxxi, 153; and *Lubarsch*, ibid., p. 187.

When brought in direct contact with various chemical disinfectants it is readily killed, but when inclosed in mucus, as in sputum, it may be quite resistant. If in a thin layer and not protected by glass, it is killed by an exposure of a few minutes to direct sunlight. If in dust, however, and protected from light, individual bacilli may retain their viability for a long time.[1] In the moist condition, the bacilli may be killed by an exposure of ten to fifteen minutes to 70° C.

Cultures can be continued indefinitely from generation to generation with a slowly diminishing virulence which finally is largely lost. Under certain conditions the virulence may be restored or enhanced by successive inoculations into susceptible animals.

The tubercle bacillus does not, so far as we know, grow in nature outside of the bodies of men and certain warm-blooded animals. It is thus apparently strictly parasitic.

Inoculation of various animals, especially of guinea-pigs, rabbits, and monkeys, may be followed by lesions similar to those of man.

Methods of Staining the Tubercle Bacillus.

In Fluids.—For the examination of fluids, such as sputum,[2] etc., the material should be spread in a thin layer on a cover-glass, dried in the air, and then passed thrice through the flame

While, as has been said above, the tubercle bacillus is stained much less easily with the aniline dyes than are most bacteria, it can be deeply colored by the use of accessory agents which intensify the stains or render the protoplasm of the bacilli more accessible to them. But when once stained the tubercle bacillus clings with great tenacity to its color in the usual decolorizing agents.

A variety of methods are in vogue for staining the tubercle bacillus, Ziehl's solution being the most useful. This is made by adding to a 5 per cent. aqueous solution of carbolic acid about one-tenth its volume of saturated alcoholic solution of fuchsin. This carbolic fuchsin will keep unchanged for a long time.

The prepared cover-glass is floated in a watch-glass or porcelain capsule—specimen side down—on this coloring fluid, and gently heated almost to boiling for from three to five minutes.

The entire specimen is thus completely stained, tubercle bacilli, tissue elements, and other bacteria which may be present, all in the same way. The next step is to remove the color with acid from all the structures which may be intermingled with the tubercle bacilli; the latter, owing to the tenacity with which they retain the stain, being but slightly affected. This is done by dipping the cover-glass into an aqueous or alcoholic solution of 5 per cent. sulphuric acid, and shaking it about for a few seconds. Under the influence of the acid the specimen on the cover-glass loses its red color and becomes gray or colorless. It is then thoroughly rinsed in three or four successive portions of alcohol, and finally in water. By this manipulation the red color may be to a slight extent restored.

Care should be taken not to expose the specimen too long to the action of the acid, because then the bacilli also may be partially or completely decolorized. A little experience will enable the experimenter to judge of the proper time for the action of the acid. The specimens may be studied immediately after drying with the use of an oil immersion lens, or they may be mounted in balsam before examination.

Inasmuch as some bacteria besides the tubercle bacilli not infrequently retain a slight red color, it is well, after the specimen is rinsed in water, to float the cover-glass for a few minutes in a dilute aqueous solution of methylene blue, which will replace the red color in all of the bacteria except the tubercle bacilli. There is thus secured a marked contrast between the tubercle bacilli, which are red, and other bacteria, which are blue. The contrast stain should not be intense.

[1] For a study of the viability of the tubercle bacillus, see *Rosenau*, Bull. No. 57, Hyg. Lab., U. S. Pub. Health and Mar.-Hosp. Serv., Washington, 1909.

[2] It is well in obtaining sputum for examination in cases of suspected pulmonary tuberculosis to secure that which has been raised during several hours, including the early morning discharge.

Pappenheim's Method.—After staining in the hot carbol-fuchsin as above, the specimen is immersed, without washing, in a solution of 1 per cent. rosolic acid in 95 per cent. alcohol saturated with methylene blue, to which 20 per cent. of glycerin has been added. After ten minutes in this solution the specimen is washed in water, dried, and mounted. By this method the tubercle bacilli are stained red, and the smegma bacilli (page 306), blue.

In Sections.—Thin sections of tuberculous tissue which has been hardened in alcohol are stained in the same way, except that instead of drying and fixation by heat the sections are fixed to the cover-glass by means of egg albumen, and then cover-glass and section are manipulated together.

When differentiation is complete, the section is cleared in oil of origanum and mounted in balsam.

For purposes of simple recognition of the bacilli in sections it seems to the writer usually better to have no color in the preparation other than that which the tubercle bacilli possess. But it is often convenient to demonstrate the nuclei of the cells at the same time, and this may be accomplished by staining lightly afterward with a dilute solution of some color which will contrast with that of the bacilli, such as methylene blue.

In the examination of *urine* for the presence of the tubercle bacillus it is well to collect the sediment by means of a centrifugal machine. In the examination of milk or other fat-containing fluids for tubercle bacilli, it is well, after the film has been formed upon the cover-glass and before staining, to rinse with chloroform followed by alcohol, and this by water.

Occasionally one finds in urine acicular crystalline bodies considerably resembling the tubercle bacillus in size and shape, and retaining a red color after the decolorization of the specimen. A careful study of the form, however, will suffice to prevent mistakes.

The only other bacilli which are liable to be mistaken for the tubercle bacilli are the bacillus of leprosy and the so-called smegma bacillus which sometimes occurs beneath the prepuce. The lepra bacillus may be distinguished from the tubercle bacillus by the following differential staining process: If the lepra bacillus be stained for ten minutes in a dilute alcoholic solution of fuchsin (five drops of saturated alcoholic solution of fuchsin to 3 c.c. of water), and then rinsed for a few seconds in a solution of nitric acid (one part) in alcohol (ten parts), it will retain a red color, while under the same treatment the tubercle bacillus remains uncolored.

Antiformin in Sputum Examinations.—Antiformin is a patented preparation containing sodium hydroxide and sodium hypochlorite. When mixed with sputum in such proportion that the antiformin is present in about 15 per cent. the sputum is softened and most bacteria except the tubercle bacilli are killed. After the softening of the sputum it is diluted with water or alcohol and spun in the centrifuge, the sediment is gathered and respun, and the final sediment is used for smears and stained in the usual way. By the use of antiformin and centrifugation a "concentrate" of the bacilli from sputum may be secured for diagnostic inoculation of guinea-pigs or for culture, if the use of alcohol as a diluent is avoided.

Varieties of Tubercle Bacilli.

While many of the lower animals are susceptible to inoculation with human tubercle bacilli, the organisms obtained from such animals may present noteworthy biological variations from the human type. Even so long ago as 1868, Villemin called attention to the fact that none of the rabbits inoculated with human tubercle presented so rapid and generalized a disease as that which was noticed when tuberculous material from the cow was used. More recently, Theobald Smith again called attention to the marked biological peculiarities which separate the bovine bacillus from the human type.[1]

[1] See *Smith, Th.*, Jour. Med. Research, 1905, N. S. viii, 253; also *Wolbach, S. B.*, and *Ernst, H. C.*, Jour. Med. Research, 1903, N. S. v, 313 (bibl.); and *Cobbett*, The Causes of Tuberculosis, Cambridge, 1917 (bibl.).

At present three groups are well recognized: the human, the bovine, and the avian types of organism,[1] the last of which plays but a small part in human pathology. A fourth group, that known as the fish tubercle bacillus or tubercle bacillus of cold-blooded animals, is still somewhat doubtfully classed with the group of tubercle bacilli which occur in the mammalia. In other words, it has not yet been satisfactorily demonstrated that these tubercle bacilli of cold-blooded animals are the cause of certain pathogenic lesions with which they are associated.

Of considerable importance in human pathology is the differentiation of the human and bovine types, as such determination not infrequently leads to a more or less complete demonstration of the source of the infection. The morphological characters of the two groups are quite similar. The tubercle bacilli of both types vary a great deal in length and diameter, and no constant difference has been determined which is of any value. There are, however, marked differences in the growth rate on suitable culture media. The human type of tubercle bacillus is eugonic, that is, it grows easily on suitable soil, while the bovine bacillus is dysgonic and grows very poorly as compared to its human relative. Nevertheless, after long cultivation on suitable media, the growth rate of the two approach each other, and the difference may be marked only in the primary culture. On blood serum to which 2 per cent. to 5 per cent. of glycerin has been added, the human strain grows very well, while the bovine strain grows with difficulty. This is probably due to the difference in their capacity for making use of glycerin. The same variation is observed with glycerin-agar on which the human type of bacillus ultimately grows very luxuriantly, while the bovine type never does. Glycerin-egg and glycerin-potato media also afford valuable means of differentiating the organisms, the same variations being shown.

While these cultural differences are sufficient to enable an expert to distinguish the two types of organisms, a check is usually employed by the inoculation of an animal of differing susceptibilities to the two types. The most convenient is the rabbit, which is fairly resistant to infection with the human tubercle bacillus and very susceptible to that with the bovine type. After intravenous injection of organisms of the latter form, the animal will often be studded with large and small tubercles, the size depending somewhat upon the length of time which it has been allowed to live after the injection; and this result can be obtained by the intravenous injection of not over 0.01 mg. of tubercle bacilli from a pure culture. If a smaller quantity of human organisms is injected, the result may be minimal, and the animal will probably not die. Intraperitoneally 1 mg. of pure culture may be employed in this differential inoculation.

Toxic Products of Tubercle Bacilli.

While there is evidence that some soluble toxic substances are given off from the tubercle bacillus in its growth and activities, it is to its specific body protein that its chief poisonous capacities seem to be linked.[2]

It has been found that tubercle bacilli which have been killed by boiling or otherwise, when introduced into the body of the rabbit either beneath the skin, or into the serous cavities, or into the blood-vessels and the air spaces of the lungs, are capable, as they slowly disintegrate, of stimulating the cells of the tissues where they lodge to proliferation, and to the production of new tissue morphologically similar to tubercle tissue in its various phases[3] (Fig. 162). Necrosis of the new-formed

[1] For bibliography of animal tuberculosis, see *Eber, A.* Lubarsch u. Ostertag, Ergebn. d. allg. Path., 1917, xviii,[2] 1 (bibl.). For a study of avian tuberculosis, see *Hastings, Halpin,* and *Beach,* Jour. Infect. Dis., 1913, xiii, 1; also *Himmelberger,* Centralbl. f. Bakteriol. I. Abt., Orig., 1914, lxxiii, 1.

[2] For a study of certain toxic products of the tubercle bacillus, see *White, B.,* and *Avery, O. T.,* Jour. Med. Research, 1912, N. S. xxi, 317.

[3] For further details concerning the effects of dead tubercle bacilli in the body, see *Prudden* and *Hodenpyl,* New York Med. Jour., 1891, liii, 637, 697; and *Prudden,* ibid., liv, 617. See also *Herxheimer,* Zieglers Beitr., 1903, xxxiii, 363 (bibl.); and *Miller, J.,* Jour. Path. and Bacteriol., 1905, x, 351 (bibl.).

cells may occur, but this differs in some respects from the coagulation necrosis induced under the usual conditions. Dead tubercle bacilli are also markedly chemotactic and capable of causing local suppuration and abscess.

It would seem probable then that while the power of the tubercle bacillus to induce necrosis and the fever which, in many cases, indicates a systemic intoxication, may be due to metabolic products of the living germ, the local lesions characteristic of exudative and productive inflammation may be due to a peculiar bacterial protein which is set free by the disintegration of the bacilli in the tissues. But the products of autolysis in the necrotic tissue cells may contribute to the toxemia. It is not improbable that, in addition to the protein of the tubercle bacillus, the waxy substance which the cell body contains plays an important part in determining the morphology of the lesion produced by the organism.[1]

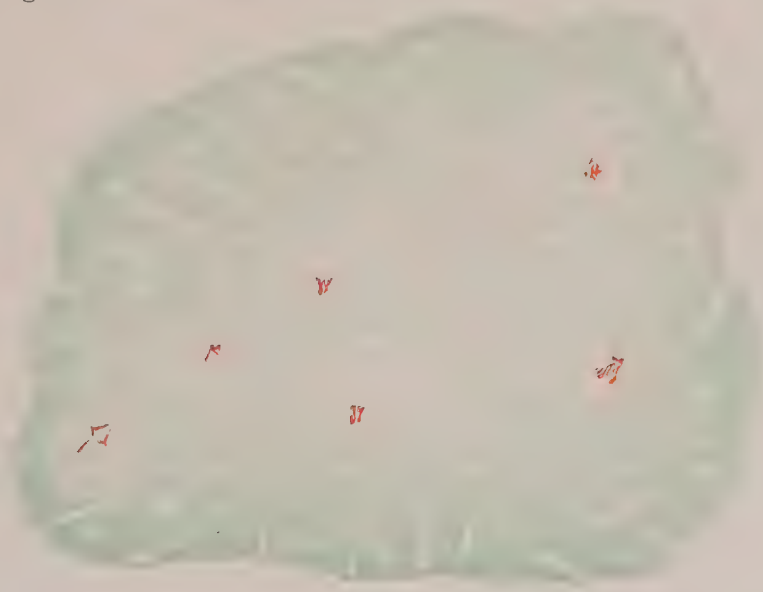


FIG. 162.—INFLAMMATORY NODULE (PSEUDOTUBERCLE) IN THE LIVER OF THE RABBIT INDUCED BY THE INTRAVENOUS INJECTION OF DEAD TUBERCLE BACILLI.

Most of the dead bacilli have disintegrated, setting free the bacterial protein which has stimulated the new cell growth. A few fragments of the bacilli, however, still remain.

Agglutinating Substances.

The serum of tuberculous animals and men may contain agglutinating substances. The reaction, however, frequently fails and is not at present of much diagnostic value.

Complement Fixation.

The use of the method of complement fixation[2] has been developed recently as a means of diagnosis, and is of great value as indicating only an active and fairly ex-

[1] *Morse, P. F.*, and *Stott, E.*, Jour. Lab. and Clin. Med., 1916, ii, 159.

[2] *Craig, C. F.*, Jour. Am. Med. Assn., 1917, lxviii, 773; *Miller, H. R.*, ibid., 1916, lxvii, 1519; Jour. Lab. and Clin. Med., 1916, i, 816; and *Burns, Slack, Castleman*, and *Bailey*, Jour. Am. Med. Assn. 1917, lxviii, 1386. *Brown, L.*, and *Petroff, S. A.*, Amer. Rev. Tuberculosis, 1918, ii, 525.

tensive process. Reactions are not given in the case of latent foci as with the allergic tests, which are so sensitive as to be of but little value except as excluding tuberculosis.

A good deal of the success of the method seems to depend upon the choice of a proper antigen. The most efficient so far obtained appears to be that prepared by grinding the tubercle bacilli with table salt in a suitable container until the organisms are thoroughly disintegrated, and then adding distilled water to isotonicity.

Tuberculin.

When the tubercle bacillus is grown on glycerinated nutrient broth certain metabolic products are formed and pass into solution in the fluids. If after some weeks of vigorous growth the germs are separated by filtration and the broth is concentrated by evaporation, a dark brown fluid results which is called *tuberculin*. This substance —at one time believed by many, and still by a few observers, to possess distinct curative properties in certain forms of tuberculosis—has assumed great economic importance on account of its value as a diagnostic agent in bovine tuberculosis. For if administered subcutaneously in small quantity to cattle a marked temperature reaction follows in tuberculous animals, while those which are sound are unaffected. The existence of even very slight lesions may be detected in this way. In man also tuberculin has proved of value in cases in which the efforts to establish a diagnosis by the usual methods have failed. The new tuberculin "T. R." contains the dead bodies of tubercle bacilli.[1]

The cutaneous tuberculin test of von Pirquet[2] consists in the application of a small quantity of Koch's original tuberculin to a superficial abrasion of the skin. The skin of the forearm is cleansed with alcohol and dried, and three abrasions are made, about two inches apart. A drop of undiluted tuberculin is then placed on the upper and the same amount on the lower abrasion, the excess being wiped off with cotton at the end of ten minutes. The middle abrasion serves as a control. In a negative reaction, which indicates that the patient has no tuberculosis, there is no change in the color of the treated areas as compared with the control. If the patient is tuberculous a reddening appears in twenty-four to forty-eight hours, which in a very severe reaction may go on to vesiculation. In persons with very active tuberculosis the reaction may be only infiltration with but little or no redness.

Immunity and Therapeutic Use of Tuberculin in Tuberculosis.

The fact that so large a percentage as from sixty to ninety of human beings dying from all causes have been shown by autopsies to have been at some period and in some measure affected with tuberculosis, while the mortality from tuberculosis as compared with death from all other causes is not far from fourteen per cent. indicates that man enjoys a marked degree of natural immunity to the incursions of the tubercle bacillus. The clinical data are not very convincing as to the acquirement of increased immunity after successfully coping with the disease. However, experiments on animals, those of Trudeau and others, showed that by the repeated inoculation of small doses of tubercle bacilli of attenuated virulence, rabbits may be largely protected, though not rendered wholly immune, from the full effect of later injections of virulent bacilli. By intravenous injections of some product or derivative of the tubercle bacillus, Behring has apparently succeeded in rendering young cattle highly, and it is claimed permanently, immune. Similar results have been obtained by others.[3]

Many attempts have been made to secure artificial immunity in man either by the injection of products of the growth of the tubercle bacillus, or by the use of the dead bodies of the bacilli. Wright and his followers have reported marked success in the use of a form of tuberculin which contains the bodies of the dead bacilli, especially

[1] For a résumé of various tuberculin preparations, see *Hiss* and *Zinsser*, Text-book of Bacteriology, 5th ed., New York, 1922.

[2] *von Pirquet*, Berl. klin. Wchnschr., 1907, xliv, 699.

[3] See review of animal immunization against tuberculosis, *Pearson*, Second Ann. Rept. of the Phipps Inst., 1905, p. 311.

in localized tuberculosis. This is administered in accordance with the indications of a rise or fall of the "opsonic index" of the serum (see page 219), determined by the degree of phagocytosis, the opsonic index marking the immunizing effect of the injection. Trudeau also obtained favorable results from artificial immunization with dead bodies of the bacilli, "T. R.," controlling the administrations of the very potent agent by careful clinical observations.

Altogether, then, it appears that a certain measure of active artificial immunity to tuberculosis may be secured in man. Attempts to secure passive immunity in tuberculosis by alleged antitoxic sera do not seem to have been notably successful.[1]

Complex Factors in the Tuberculous Process.

It is well in studying the characters of tuberculous inflammation to remember that in its progressive phases there are two factors at work: first, those which lead to cell proliferation and new tissue formation, which is apparently a reparative and conservative process; second, those which are inhibitory or damaging or destructive; and, also, that both sets of factors are commonly active together. It may still be considered doubtful whether the tubercle bacillus furnishes a direct formative stimulus, or whether such is furnished by damaged cells, or whether the cell proliferation may not be an expression of reparative activity in the presence of damaged tissue made possible by disturbed organic control (see page 393). In any event the new tissue which forms under the influence of the tubercle bacillus apparently owes its morphological as well as biological characteristics to impulses toward tissue formation which are exerted in the presence of agencies—doubtless poisons—restraining within narrow bounds the new connective-tissue growth, no matter how extensive or persistent this may be, and tending constantly to its destruction.

It is interesting in this connection to note that when lesions in many respects similar to those of the ordinary tuberculosis are induced experimentally in animals with dead tubercle bacilli (see above), the poisonous substances leading to necrosis are not produced continually and for indefinite periods, as is the case in infection with living bacilli, but are soon exhausted, so that after a certain amount of initial necrosis the new tissues go on to develop in the usual reparative way, blood-vessels are formed, and healing by a cicatrix under favorable conditions regularly takes place. It is probable that effective healing in tuberculosis in man takes place only after the local production of destructive poison ceases through the death or complete lysis, or, at any rate, the diminished virulence of the tubercle bacilli present.

On the other hand, it is important to bear in mind that while the formation of new cells and tissue on the part of the body in tuberculosis marks a protective adaptation to new and harmful conditions, the tubercle bacilli themselves are also subject to adaptive changes which on their side are protective. Thus, through what has been called selective adaptation of both host and microbe, a condition of balanced parasitism may be brought about in which there may be a reduced mortality, but not a reduced morbidity, since in the processes of adaptation the microbe has won capacities for harm which may be very potent and significant in individuals not adapted to it.[2]

The Number of Tubercle Bacilli in Lesions.

The number of bacilli which are present in the lesions of tuberculosis is subject to great variation. They are usually abundant in the walls and contents of phthisical cavities, and in tubercle tissue which is undergoing cheesy degeneration and disintegration. In these situations they may be found in myriads, forming sometimes a large part of the disin-

[1] See for the bearing of the parasitism of the tubercle bacillus on infection and immunity *Th. Smith* Jour. Am. Med. Assn., 1906, xlvi, 1247.

For an admirable review of our knowledge of some problems of tuberculosis, see *Th. Smith*, Jour. Am. Med. Assn., 1917, lxviii, 669.

[2] For a consideration of the mutual relationship of microbe and host, see *Th. Smith*, Jour. Am. Med. Assn., 1906, xlvi, 1247.

tegrated mass. They are found in cells and scattered among them. Sometimes they are present in considerable numbers in the giant cells of miliary tubercles. In the acute general tuberculosis of children they are often present in large numbers, particularly in the lungs (Fig. 158). They may be found in tuberculous inflammation in any part of the body, and are occasionally demonstrable in the blood. The demonstration of tubercle bacilli in the circulating blood can be made in a small proportion of cases of tuberculosis other than those of the miliary type.[1] In the latter, tubercle bacilli can be found in about 65 per cent. of cases.[2] The bacilli are constantly discharged in the sputa of patients suffering from pulmonary tuberculosis, often in enormous numbers—from one to four billion in twenty-four hours, according to Nuttall's estimate—and their presence sometimes affords valuable diagnostic aid in early stages or in obscure forms of the disease.

The number of bacilli required to infect man is not known; but in the case of a susceptible animal, such as a small guinea-pig, for instance, the inhalation of from five to twenty bacilli is sufficient to set up a tuberculous process. On the other hand, the feeding of as many as 20,000 bacilli has failed to cause an infection in the same animals.[3]

Under a variety of conditions, especially in the older tuberculous lesions, the bacilli may not be demonstrable. This apparent occasional absence of the bacilli is probably due either to their disappearance as the process grows older or to some unknown changes which interfere with the ordinary staining procedures. Much has introduced a special modification of Gram's staining method by which granules may be demonstrated in tubercle tissue not showing bacilli with the ordinary technique.[4]

On the other hand, tuberculous lesions of characteristic morphology containing easily demonstrable bacilli may not give rise to infection when injected into animals nor yield bacteria to culture, the organisms evidently being dead. This occurrence is most frequent in the cervical and peritoneal lymph-node tuberculoses of children, due very often to the bovine type of bacillus. The bronchial nodes usually give positive results after animal inoculations and the organisms so obtained are of the human type.

Frequency of Tuberculosis in Man and the Lower Animals.

Tuberculosis is a very common disease not only of man[5] but also of many of the lower animals, especially of cattle, and inasmuch as the

[1] For a study of tubercle bacilli in the blood, see *Anderson*, Bull. No. 57, Hyg. Lab., U. S. Pub. Health Serv., Washington, 1909: *Klopstock* and *Seligmann*, Ztschr. f. Hyg., 1913, lxxvi, 7; and *Klemperer*, Berl. klin. Wchnschr., 1914, li, 436.

[2] *Clough, M. C.*, Bull. Johns Hopkins Hosp., 1917, xxviii, 363. See, however, *Austrian, C. R.*, and *Hamman, L.*, ibid., 1915, xxvi, 293.

[3] See *Findel*, Ztschr. f. Hyg. u. Infectionskrankh., 1907, lvii, 104; and *Pfeiffer* and *Friedberger*, Deutsch. med. Wchnschr., 1907, xxxiii, 1577.

[4] *Much, H.*, Berl. klin. Wchnschr., 1908, xly, 691. See, also, *Hiss* and *Zinsser*, Text-book of Bacteriology, 5th edition, New York, 1922, p. 588

[5] Carefully prepared statistics show that tuberculous lesions are present in more than 90 per cent. of bodies examined at autopsies. See for a thorough and suggestive analysis of five hundred autopsies *Naegeli, O.*, Virchows Arch., 1900, clx, 426; also *Necker*, Verhandl. d. deutsch. path. Gesellsch., 1904, viii, 129. For a study of frequency of tuberculosis in children, see *Winkler*, Verhandl. d. deutsch. path. Gesellsch., 1904, viii, 118.

victims of this disease, both men and animals, are apt, as stated above, to throw off enormous numbers of the bacilli in the sputum and other excreta, the germ is widely dispersed in inhabited regions, especially in buildings frequented by uncleanly tuberculous persons or by infected cattle.

Among the lower animals, guinea-pigs, rabbits, monkeys in confinement, and cattle are particularly susceptible to the action of the tubercle bacillus. Although tuberculosis is widespread in man, he is not, as compared with some of the lower animals, particularly susceptible. While the tuberculous process presents some differences in different animal species in rate of development, amount of necrosis, tendency to softening, calcification, etc., the fundamental effects are similar in man and in the lower animals.

Portals of Entry, Distribution of Lesions, and Sources of the Tubercle Bacilli.

Portals of Entry and Distribution.—The question of the chief portals of entry of the tubercle bacillus has given rise to much discussion and much experiment. So far as concerns the lungs, in which tuberculosis is common, it has been assumed that infection is most frequently direct, the bacilli gaining access through the respiratory passages to the alveoli. Others have contended that lung infection is most often secondary to the entrance of the bacilli through the gastrointestinal canal with or without local lesions. Still others believe that tuberculosis of the lung is commonly secondary to tuberculous lesions of the bronchial lymph-nodes, or that the bacilli may enter through the tonsils, or that they often enter through the placenta. To the advocates of the latter views the blood-vessels and lymphatics play a predominant rôle in the distribution of the infective agents.

While it is probable that all of these portals of entry are of importance, it would seem well established that direct inhalations are the most frequent occurrence, while entrance through the intestinal mucosa is very common, especially in infancy.[1]

We may assume, then, that the tubercle bacillus most frequently enters the body through the respiratory organs, including tonsils and pharynx, and through the gastrointestinal canal. Traumatic infection through the skin is of relatively infrequent occurrence, as is apparently the congenital transmission.[2]

[1] For a full discussion of this subject, see *Lubarsch*, Fortschr. d. Med., 1914, xxii, 669, 701. For experimental tuberculosis in young guinea-pigs with reference to portals of entry, see *Bartel* and *Spieler*, Wien. klin. Wchnschr., 1905, xviii, 155; 1906, xix, 25. For a résumé of studies on the tubercle bacillus and its portals of entry, see *Baumgarten*, Verhandl. d. deutsch. path. Gesellsch., 1906, ix, 5; *Aufrecht*, Pathologie und Therapie der Lungenschwindsucht, Vienna, 1908; *Ravenel*, Am. Jour. Med. Sc., 1907, cxxxiv, 469. For mode of tubercle bacillus infection in young, see *Westenhoeffer*, Berl. klin. Wchnschr., 1904, xli, 153 and 191. For intestinal origin of pulmonary tuberculosis, see *Calmette* and *Guerin*, Ann. de l'Inst. Pasteur, 1905, xix, 601; and *Calmette*, Med. Rec., 1908, lxxiv, 741. For a study of mode of infection of the lungs by way of the mouth and pharynx, see *Beitzke, H.*, Virchows Arch., 1906, clxxxiv, 1.

[2] For a study of placental and congenital tuberculosis, see *Warthin* and *Cowie*, Jour. Infect. Dis., 1904, i, 140.

In adults the lungs, in children the bronchial lymph-nodes, are the most frequent seat of tuberculous lesions.[1]

Many observations on the occurrence of tuberculous bronchial, cervical, and mesenteric lymph-nodes in persons exhibiting no appreciable tuberculous lesions elsewhere would indicate the frequency of access of the bacilli to the lymph-channels without primary lesion at the portal of entry in the pharynx, tonsils, respiratory passages, intestinal mucosa, or elsewhere (see page 683). A considerable percentage of persons dying from other diseases have been found to have tuberculous lesions, often healed, in the lungs or bronchial lymph-nodes.

Sources of Tubercle Bacilli.—Tubercle bacilli are frequently transmitted to the well from the victims of tuberculosis by means of the sputum which is cast off and allowed to dry, and becoming pulverized is then inhaled as dust.

But this source of infection is perhaps not as significant as was formerly believed from analyses of material gathered from walls and floors of contaminated rooms. For it has become clear that not all the infectious material which may be cast out of the body as sputum is always readily and speedily transformed into dust. In the drying of the mucus with which much of this material is mingled, a process ordinarily rather slow, the bacteria are closely imprisoned so that only under certain conditions, such as the rubbing and beating of soiled clothing, the shuffle and tread of feet over contaminated floors, dry sweeping, and the like, is the excretion sufficiently comminuted to float in the air as dust. Even when this is the case, it has been found that a large part of such pulverized excreta is still in too large particles to remain long suspended in the air.

This condition of affairs was not appreciated in the earlier studies on dust infection, and in many instances the material called dust, collected in various places for analysis, was evidently not in such form as would have remained long in suspension. Thus it is that while the earlier identification of various pathogenic microorganisms in the dust of rooms was correct, the inference as to the constant risk of dust infection in such places was frequently at least somewhat overestimated.

On the other hand, Flügge and others[2] have found that not only in sneezing and coughing, but also in ordinary speech, the secretions of the nose, mouth, and throat may be cast forth in considerable quantity for a distance of several feet, not only in the form of visible droplets, but as a more or less abundant, invisible spray, which may remain suspended for from half an hour to several hours, and may be carried for long distances on such slowly moving air currents as are common in inhabited rooms.

Thus, fully virulent, infectious material may be transmitted directly through the air in coughing and sneezing, indirectly through dried

[1] For studies in the frequency, localization, and modes of dissemination of tuberculosis, with special reference to its occurrence in the lymph-nodes and during childhood, see *Harbitz*, Jour. Infect. Dis., 1905, ii, 143 (bibl.). For a study of localization in infants and young children, see *Wollstein*, Arch. Int. Med., 1909, iii, 221.

[2] For the studies of *Flügge* and his assistants, see Ztschr. f. Hyg. u. Infectionskrankh., 1899, xxx, 107; 1901, xxxviii, 1.

infectious sputum ground to dust and floating in the air. Less frequent is the conveyance of tubercle bacilli through soiled utensils. The transmission of this germ through contaminated milk[1] and the meat of tuberculous cattle[2] is a mode of infection of great importance, especially when such contaminated milk is taken by young children.

Whichever way the tubercle bacilli enter the body, whether directly into the lungs, or by the pharynx or tonsils, or through the intestinal mucosa, or in rarer cases through wounds or through the placenta, they are transported by the blood- and lymph-vessels to lymph-nodes or to the tissues, where they lodge and grow and incite the formation of tubercles. These, again, if in the blood- or lymph-vessels when they soften and set the bacilli free by ulceration into the channels, afford fresh foci of distribution. So that in cases of disseminated tuberculosis the process of distribution is more or less gradual. In the meantime the progress of the lesions dependent in their topography upon the fortuitous character of the distribution of the infective agent is marked by the protective adaptation of the body-cells expressed by the formation of the tubercles and the development of immunizing substances; while, on the other hand, the bacillus itself is undergoing these adaptative modifications of its own biological characters which are expressed in what we call its virulence.

Statistics show, as we have seen, that in the majority of cases in man the protective agencies of the body suffice to localize the lesions, surround the bacilli by necrotic masses in which they do not flourish, or inclose them in a fibrous envelope. Thus it appears that it is largely the chances of a wide or a continued distribution of the infective agent, or an unusual susceptibility of the host, or exalted virulence of the bacilli, or the occurrence of fresh infection, that makes tuberculosis now and then so formidable a malady to man.

While it is not impossible that future research may lead to the development of effective methods of artificial immunization to tuberculosis, it is to preventive measures that we must look for the largest success in the suppression of this scourge of the human race. By proper disposal of the sputum; by providing against aerial dispersion of infective material through unguarded coughing and sneezing; and by such intelligent methods of cleaning and disposal of dust as shall safeguard the respiratory organs; together with an enlightened supervision of the supplies of meat and milk, it should be possible even in crowded communities largely to reduce both the morbidity and the mortality of tuberculosis.[3]

Concurrent Infection in Tuberculosis.

A concurrent infection with the tubercle bacillus and the pyogenic microorganisms is of extreme significance in that phase of tuberculous inflammation of the lungs commonly called phthisis.[4] While the so-called cold abscesses may be caused by the tubercle bacillus alone, this

[1] Many cases of infection of human beings, especially of children, with bovine bacilli, have been reported and in children abdominal tuberculosis and tuberculosis of the cervical lymph-nodes are most frequent. Park estimates that about 10 per cent. of tuberculosis in children under five years is due to bovine infection. See, for tables of observation, *Park* and *Williams*, Pathogenic Microorganisms, 8th ed., New York, 1924, p. 434; for a most comprehensive study of the question of types of organism and portals of infection, *Cobbett*, The Causes of Tuberculosis, Cambridge, 1917; and for study of bovine and human types of tubercle bacilli, *Park, W. H.*, and *Krumwiede, C.*, Jour. Med. Research, 1910, N. S. xviii, 205; 1912, N. S. xxii, 109. See also *Lewis*, Jour. Exper. Med., 1910, xii, 82; *Mitchell, P.*, Brit. Med. Jour., 1914, i, 125; and *Fraser*, Jour. Exper. Med., 1912, xvi, 432.

[2] See *Kober*, Am. Jour. Med. Sc., 1903, cxxvi, 684 (bibl.). For the intercommunicability of human and bovine tuberculosis, see *Ravenel*, Proc. Path. Soc., Philadelphia, 1902; also résumé by *Bovaird*, Med. Rec., 1905, lxvii, 283.

[3] For a study of tubercle bacilli on books, see *Mitulescu*, Ztschr. f. Hyg. u. Infectionskrankh., 1903, xliv, 397.

For a study on flies and tuberculosis, see *Lord*, Boston Med. and Surg. Jour., 1904, cli, 651.

[4] See *Spengler*, Ztschr. f. Hyg. u. Infectionskrankh., 1894, xviii, 343 (bibl.); and *Prudden*, New York Med. Jour., 1894, lx, 1.

germ is not infrequently found under these conditions to be associated with other pyogenic microorganisms, especially the streptococcus and staphylococcus. In addition to the concurrent infection of the tissues, organisms of the streptococcus, staphylococcus, and pneumococcus groups may occasionally be demonstrated in the circulating blood of persons suffering from active pulmonary tuberculosis.[1]

Bacteria Resembling the Tubercle Bacillus.

There are several species of bacteria which after deep staining resist the decolorizing action of dilute acids. These have been called, collectively, acid-resisting or acid-proof bacteria.[2] We shall consider only two of these.

The Smegma Bacillus.—This organism is often present and sometimes in large numbers in the preputial smegma and elsewhere about the external genitals. It so closely resembles the tubercle bacillus in size, shape, and staining reactions that it is liable by morphological examinations alone to be mistaken for it. It has been cultivated on artificial media and is not pathogenic. The smegma bacillus, when stained as above recommended for the tubercle bacillus, resists the decolorizing action of the acid; but it is usually decolorized by prolonged exposure to alcohol, thus differing from either the tubercle bacillus or the leprosy bacillus. But this color reaction is not certain; individual bacilli not infrequently remain unstained. Various special methods for differentiation have been suggested.[3] In doubtful cases, and when serious operative procedures are dependent upon the bacterial diagnosis, recourse should be had to animal inoculations.

The "Hay Bacillus."—This resembles the tubercle and smegma bacilli in form and staining peculiarities. It is called the "hay bacillus" or "grass bacillus" because of its common occurrence upon grass-heads in the fields. It is not pathogenic and is readily cultivated.

Similar organisms have been frequently found in milk and butter, also in the sputum in gangrene of the lung.

Lupus and Other Forms of Tuberculosis of the Skin.

Local tuberculous inflammation of the skin may occur in the form of small nodules or wart-like thickenings, as the result of accidental inoculation. Local skin infection may occur about the orifices of the body in tuberculous persons from contact with secretions or excretions containing the tubercle bacilli, or about sinuses leading to tuberculous abscesses, joints, etc., or in the vicinity of tuberculous lymph-nodes.

A chronic form of tuberculous inflammation which presents special clinical features has long been known under the name of *lupus*.

Lupus.—This form of inflammation most frequently occurs in the skin of the face, but also in the mucous membrane of the mouth, pharynx, conjunctiva, vulva, and vagina. The lesion consists of small, multiple nodules of new-formed tissue, in the cutis or mucosa and submucosa. By the formation of new nodules and a more diffuse cellular infiltration of the tissue between them the lesion tends to spread, and by the confluence of the infiltrated portions a dense and more or less extensive area of nodular infiltration may be formed. There may be an excessive production and exfoliation of epidermis over the infiltrated area, or an ulceration of the new tissue.

Microscopical examination shows the lesion to consist of small spheroidal cells intermingled with variable numbers of larger, polyhedral cells and cell masses, and in

[1] *Brown, L., Heise, F. H.,* and *Petroff, S. A.*, Trans. 9th Ann. Meeting National Assn. for Study and Prevention of Tuberculosis, 1913.

[2] See for résumé and bibliography *Abbott* and *Gildersleeve*, Tr. Assn. Am. Phys., 1902, xvii, 37; also *Rosenberger*, Proc. Path. Soc., Philadelphia, January, 1904.

[3] For a critical review, see *Dahms*, Jour. Am. Med. Assn., 1900, xxxiv, 983 (bibl.). Consult also *Cowie*, Jour. Exper. Med., 1900, v, 205

For the method of *Pappenheim*, which is said to be more reliable than the alcohol decolorization, see p. 297.

many cases giant cells (Fig. 163). In some cases a well-marked reticulum is present between the new cells, and these are often grouped in masses around the blood-vessels. In some cases there is, without previous ulceration, a formation of new connective tissue in the diseased area, and a well-marked cicatrization; in other cases the cells and intercellular substance undergo a disintegration which leads to ulceration. Tubercle bacilli in small numbers may be found in these lesions. In the clinical group of diseases called lupus there are other forms of lesion which are not incited by the tubercle bacillus.

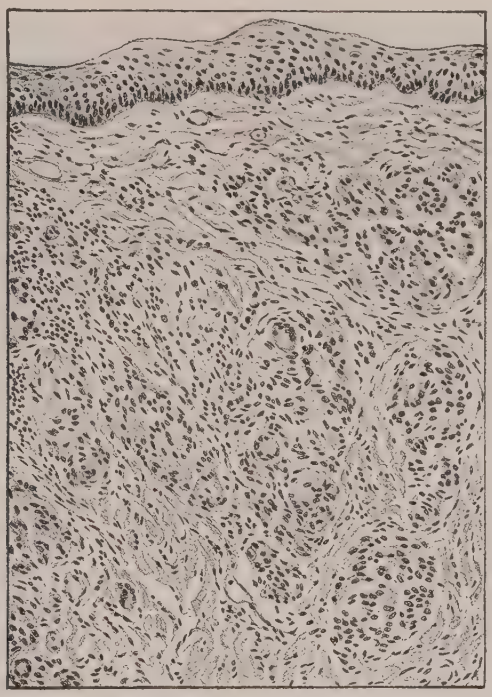


Fig. 163.—Lupus of Face.

Bibliography of Tuberculosis.

The announcement of the discovery of the Bacillus tuberculosis by *Koch* was made in the *Berliner klinische Wochenschrift*, 1882, xix, 221. A most elaborate and valuable article on the same subject by *Koch* is contained in the Mittheilungen aus dem Kaiserlichen Gesundheitsamte, 1884, ii, 1.

In the large work of *Straus*, La Tuberculose, Paris, 1895, the experimental aspects of the subject are fully considered.

In the work of *Cornet*, Die Tuberculose, Vienna, 1907, together with the general and clinical consideration of the disease, the modes of infection and prophylaxis are set forth, with bibliography. See also Kolle and Wassermann, Handbuch der path. Mikoorganismen," 2d ed., 1913, v., 391–746. An excellent summary of the tubercle bacillus and its biological characters is in *Kolle* and *Hetsch*, Die Experimentelle Bakteriologie und die Infectionskrankheiten, 5th ed., Berlin, 1919. An extremely important work is the Handbuch d. Tuberkulose, edited by *Brauer*, *Schröder*, and *Blumenfeld*, Leipzig, 1914. One of the most valuable recent sources of information on the biology of the tubercle bacillus is *Cobbett*, The Causes of Tuberculosis, Cambridge, 1917.

LEPRA (Leprosy).

Leprosy is characterized by the development of nodular and sometimes diffuse masses of tissue, consisting of larger and smaller cells of various shapes—spheroidal, fusiform, and branched, with a fibrous stroma—the whole somewhat resembling granulation tissue. The new tissue is most frequently formed in exposed parts of the skin, as the

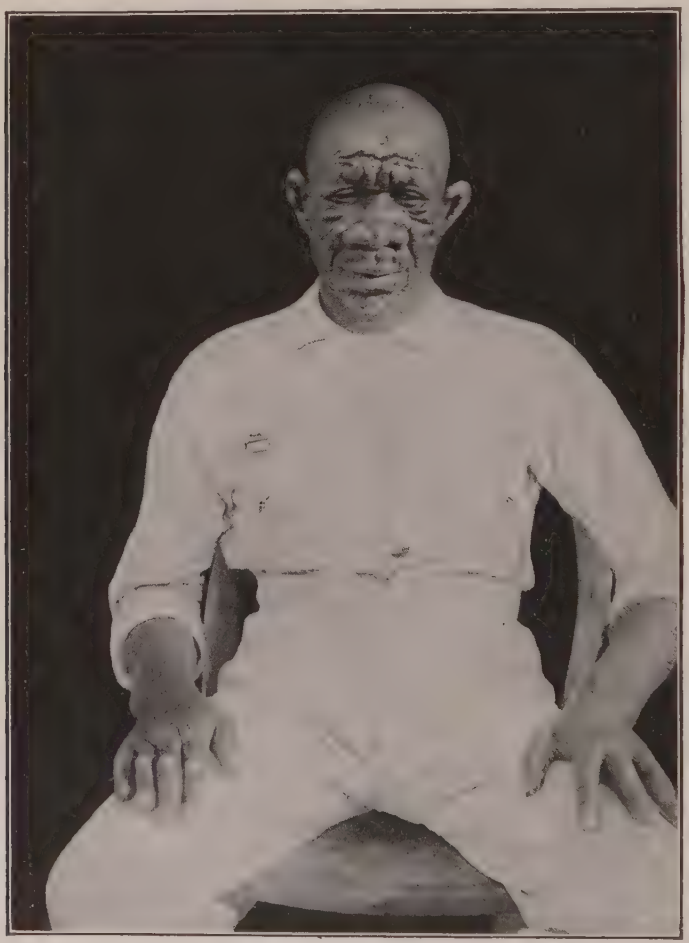


Fig. 164.—Tubercular Leprosy.

face, hands, and feet, but it may occur in the skin of any part of the body. It is formed more rarely in the subcutaneous connective tissue, in interfascicular connective tissue of nerves, in the viscera, and in the mucous membranes. The mucous membranes most frequently affected are those of the eye, nose, mouth, and larynx. The nodules may be very small or as large as a walnut, and may be single or joined together

in groups or masses. The tissue of the part in which the new formation occurs may be atrophied and replaced by, or may remain intermingled with, the leprous tissue, or it may be hyperplastic. The nodules may persist for a long time without undergoing any apparent change, or they may soften and break down, forming ulcers; but ulceration, except in the mucous membranes, is said usually to occur as the result of injury or unusual exposure. The leprous tissue may change without ulceration into cicatricial tissue, or cicatrization may follow ulceration.

Various secondary lesions and disturbances of nerve function are associated with the formation of leprous tissue in the nerves and central nervous system, and lead to various types of neuritis, perforating ulcers of the sole of the feet, etc.

In all the primary lesions of leprosy, bacilli are said to be present, mostly in the cells, and particularly in the larger transparent spheroidal forms, but sometimes free in the intercellular substance. The bacilli have been found in the skin, mucous membrane of the mouth and larynx, in peripheral nerves, in the cornea, in cartilage, in the testicles, kidney, liver, and in the blood and lymph-nodes. Sometimes the cells contain but few bacilli, but they are frequently crowded with them.[1]

Characters of the Lepra Bacilli.[2]

The bacilli are from 4 to 6 μ long and very slender. They are sometimes pointed at the ends and sometimes present spheroidal swellings (Fig. 165). In their comportment toward staining agents, as well as in general morphological characters, they considerably resemble the Bacillus tuberculosis, but they are more readily stained. They may be stained with fuchsin or gentian violet by the ordinary method, or by the method employed for staining the tubercle bacillus (see page 296).

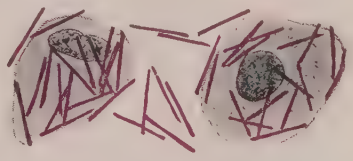


Fig. 165.—The Bacilli of Leprosy. From a nodule in the skin, showing the bacilli free and within cells.

Cultures and Pathogenesis.—Various reports of success in the artificial cultivation of the lepra bacillus have been made, the organisms described being separable into four groups: diphtheroid bacilli, acid-fast chromogenic bacilli, anaerobic acid-fast bacilli, and acid-fast non-chromogenic bacilli. The problem is complicated by the fact that a variety of organisms is undoubtedly present in the tissues in leprosy; and the possibility that the disease is due to more than one organism in symbiosis must be considered.[3]

The structure of the new tissue growth, the absence of coagulation necrosis, and the peculiar grouping of the bacilli in the large transparent cells are characters which usually clearly distinguish the lesions caused by the leprosy bacillus from those of tuberculosis.

Leprosy is common in India and in other hot countries. It is infrequent in America, but in the Gulf States, in Mexico, among the Norwegians in the Northwest, and in the eastern British provinces a con-

[1] A valuable article on leprosy is that by *Sticker, G.*, Mense, Handbuch d. Tropenkrankheiten, 2d edition, Leipzig, 1914, iii, 1.

[2] The Bacillus lepræ was first discovered by *Hansen* in 1874, and reported by him in Virchows Arch., 1880, lxxix, 32.

[3] For a critical review of the bacteriology of human and rat leprosy, see *Wolbach* and *Honeij*, Jour. Med. Research, 1913–14, N. S. xxiv, 367 (bibl.). See also *Johnston*, Philippine Jour. Sc., 1914, ix, 3.

siderable number of cases are grouped. Isolated cases are, however, encountered now and then in various parts of the United States.[1]

Communicability.—So long as the leprous tissue is intact the bacilli are closely inclosed by it. But when necrosis and ulceration occur, as on the skin or the mucous membranes, the bacilli may be widely distributed; from ulcerated nodules in the nose and pharynx, for example, in sneezing and coughing. But even persons exposed to infective exudates are so seldom infected that when infection does occur one is forced to assume special predisposing factors which we do not understand. Under proper sanitary conditions leprosy is not to be regarded as readily communicable.[2]

SYPHILIS.

It has been found convenient to consider the lesions of syphilis as occurring in three stages, *primary*, *secondary*, and *tertiary*. These stages may perhaps mark epochs in the development of the infective agent or phases in the protective action of the body-cells in the course of their adaptation to the parasitic organism; or, finally, the stages of syphilis may bear some relationship to the adaptive processes of the infective organism itself.

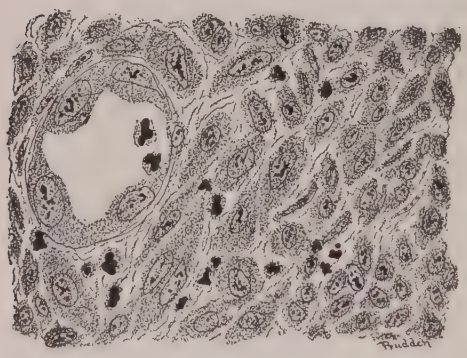


FIG. 166.—NEW-FORMED TISSUE IN SYPHILITIC INFLAMMATION.
From a hard chancre, showing swollen endothelium in a small blood-vessel.

It may be said in general that the characteristic lesions of syphilis consist in a more or less circumscribed formation of new tissue. This may be made up largely of small spheroidal cells or of these with polyhedral cells (Fig. 166), and of occasional giant cells. The new tissue, which may be diffuse or in more or less clearly circumscribed masses, contains, as a rule, few blood-vessels, and is prone to undergo coagulation necrosis. This tendency is most pronounced in the circumscribed masses.

The endothelial cells of the blood-vessels in and near the inflammatory foci in this form of inflammation are not infrequently swollen and may proliferate (Fig. 166 and 167, *B*). The vessels may otherwise undergo extensive changes.

Primary Lesions.—At the point of inoculation in a few weeks a focus of inflammation develops—the initial sclerosis. This may be in the form of a papule or a vesicle, and in either case erosion of the surface is

[1] See *Brinckerhoff*, Present Status of the Leprosy Problem in the United States, Pub. Health and Marine Hosp. Serv., Washington, 1908.

[2] For bibliography of leprosy, consult *Jadassohn*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 771.

apt to occur and a hardening of the deeper tissues, leading to the so-called *chancre*. In this primary lesion, in addition to more or less fluid and cellular exudate, there may be obliterating endarteritis, a small spheroidal-cell infiltration of the connective tissue, proliferation of connective-tissue cells, especially near the blood-vessels (Fig. 168), swelling of the vascular endothelium, and an occasional development of giant cells. This new tissue may become fibrous and the initial lesion may heal.

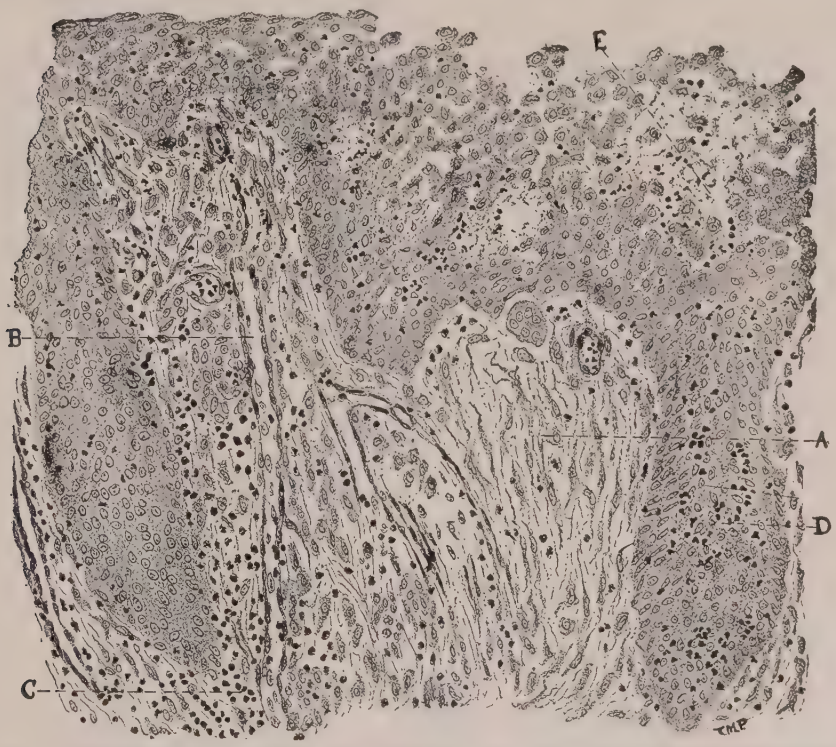


FIG. 167.—SECTION OF A PORTION OF A SYPHILITIC CONDYLOMA OF THE MUCOUS MEMBRANE.

A, Edematous papilla; *B*, swollen endothelial cells in small blood-vessels of a papilla; *C*, pus cells in the submucous connective tissue; *D*, pus cells in the epithelium; *E*, disintegration of the epithelium in the superficial portion of the mucous membrane.

Usually in connection with, or following the development of, the initial lesion there is a hyperplasia of the lymph-nodes belonging to the anatomical district of the lesion, which become hard and swollen. These hyperplastic lymph-nodes, called *buboes*, are not apt to suppurate except as the result of concurrent infection with pyogenic bacteria, and the swelling gradually subsides.

Secondary Lesions.—After six or seven weeks the so-called secondary stage of syphilis, now called constitutional syphilis, is entered upon. This is characterized by various forms of eruption on the skin and

mucous membranes—macules, papules, and pustules. Periostitis is not infrequent. At this period there often develop on the mucous membranes or where these join the skin, circumscribed areas of exudative and productive inflammation of the papillary layers with necrosis and exfoliation of the epithelium. The papillæ are enlarged, the epithelium swollen and opaque. These local areas of inflammation and necrosis are called *mucous patches*. Of similar character are the elevated areas of the skin common about the generative organs in secondary syphilis, called *condylomata*. Here also there is at the base the characteristic cell proliferation with swelling of the papillæ and thickening and exfoliation of the epithelium, and there may be an abundant infectious exudate from the surface.

Fig. 168.—Section from a Primary Syphilitic Nodule of the Mucous Membrane of the Mouth.

Showing collections of cells about the blood-vessels in the submucous tissue.

Tertiary Lesions.—One of the most characteristic phases of the tertiary inflammations of syphilis is the formation in the periosteum or in the viscera, especially in the liver, lungs, heart, brain, and kidney, of masses of new tissue called *gummata*.

The smaller gummata consist of a mass of small spheroidal and epithelioid cells (see Fig. 169). As these cell masses grow larger they are apt to become necrotic and caseous at the center, and we may then have, as seen by the naked eye, a grayish white, usually firm mass, with a more or less dense and irregular granular center and a translucent, often radially striated border of dense fibrous tissue (see Fig. 170). In the early stages, giant cells of the Langhans' type may be present in small numbers.

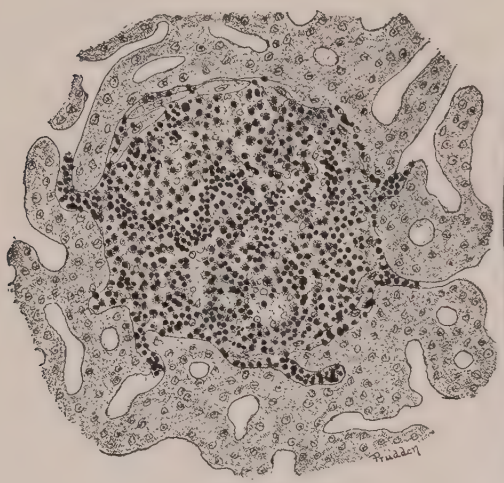


Fig. 169.

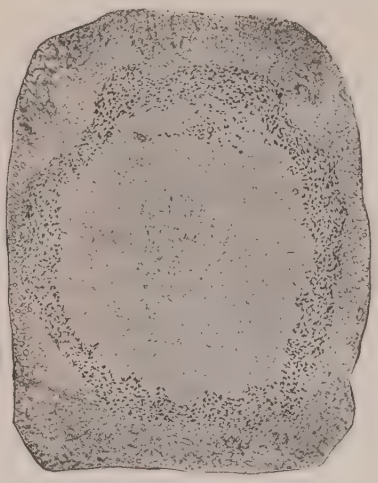


Fig. 170.

Fig. 169.—Small Nodule of Syphilitic Inflammation (Miliary Gumma) in the Liver.

Fig. 170.—Syphilitic Gumma in the Liver.

Showing necrotic caseous center merging into the new-formed cellular and fibrous tissue in the periphery. This gumma was much larger and is much less magnified in the cut than that in Fig. 169.

Gummata vary in size from those invisible to the naked eye to those several centimeters in diameter; they are usually single, but may be multiple, and occasionally several coalesce. The border zone of the gumma usually consists of granulation or fibrous tissue and may be regarded as due to the reparative reaction of the surrounding tissues. The necrotic portions of gummata may be absorbed and the whole replaced by a mass of cicatricial tissue; or strands of fibrous tissue inclosing irregular islets of caseous material may long persist at the original seat of the gummata. In some instances the syphilitic inflammation may be diffuse, with or without marked necrosis. In the lungs, the liver, and the walls of the arteries the later stages of syphilitic infection may be marked by the diffuse formation of fibrous tissue.

Congenital Syphilis.—The lesions of congenital syphilis are those of the secondary and tertiary stages, and may be present at birth or develop at a later period. Various phases of malnutrition are often obvious. There may be pemphigus of the hands and feet or elsewhere, with vesicles or blebs containing variously colored or bloody fluid. Pustules, usually about the buttocks, various erythematous rashes, coryza, inflammations

of the bones, joints, and cornea, etc., are frequent. Irregularities in the ossification of the long bones (page 1087), gummata and cirrhosis of the liver, enlargement of the spleen, various inflammatory and degenerative lesions of the kidney, and obliterating endarteritis are among the more common marks of congenital syphilis.

Diagnosis.—The nodular lesions of syphilis are in many respects structurally similar to those of tuberculosis, so that it is sometimes difficult to distinguish them on morphological examination alone. But the greater variety in the developmental stages of the tuberculous foci which may be found in a single individual, the grouping of the lesions in a manner indicative of local infections, and in the last resort the demonstration of the presence of the tubercle bacillus, will usually suffice to distinguish the tuberculous from the syphilitic lesion, even without recourse to the clinical history.

For further details regarding syphilitic lesions of the viscera see Part II. For many details regarding syphilis, its symptomatology and lesions, its effects upon gestation and the infant, etc., reference is made to special works on the subject.[1]

Animal Inoculations.—It has been shown by Metchnikoff and Roux[2] and by Neisser,[3] that successful inoculations of apes may be made with the virus of syphilis. It has been found that while cutaneous inoculation with material from primary and secondary lesions gives positive results, subcutaneous and intraperitoneal introduction of similar material does not. Rabbits also have been successfully inoculated.[4]

Treponema pallidum (Spirochæta pallida).—In 1905 Schaudinn and Hoffmann[5] described the occurrence in primary lesions of syphilis of a slender, spiral organism (Fig. 171 and 172) of about the length on the average of the diameter of a red blood-cell, which they called *Spirochæta pallida.* It is sharply curved, corkscrew like, having from three to ten or more curves, and is pointed at the ends. It is mobile, rotating on the long axis, and moving in both directions. This organism, at first called Spirochæta, was afterward renamed *Treponema.*[6]

The Treponema pallidum is stained with difficulty by the ordinary reagents and is thus frequently difficult of detection. It may be mixed, especially when on the ulcerating surfaces of syphilides, with coarser and more readily stained spiral organisms, particularly *Spirochæta refringens,* and with various other saprophytic bacteria. It was first isolated in pure culture from animal and from human lesions by Noguchi.[7]

[1] For critical summary of syphilis with bibl. to date, see *Lang* and *Ullmann*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 481; and *Herxheimer*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907, xi[1], i; and 1908, xii, 499.

For a study of blood-vessel changes in syphilis with bibl., see, *Abramow*, Zieglers Beitr., 1899, xxvi, 202.

[2] *Metchnikoff* and *Roux*, Ann. d'Inst. Pasteur, 1903, xvii, 809.

[3] *Neisser*, Deutsch. med. Wchnschr., 1904, xxx, 1369, 1431; and *Neisser* and *Baermann*, ibid., 1905, xxxi, 48.

[4] *Bertarelli*, Centralbl. f. Bakteriol., Orig. I, 1906, xli, 320.

[5] *Schaudinn* and *Hoffman*, Arb. a. d. k. Gsndhtsamte., 1905, xxii, 527; also Deutsch. med. Wchnschr., 1905, xxxi, 711.

[6] For a discussion of the nomenclature of the organism, see *Stiles, C. W.*, Jour. Am. Med. Assn., 1917, lxviii, 57; and *Pusey, W. A.*, ibid., p. 139.

[7] *Noguchi, H.*, Jour. Amer. Med. Assn., 1911, lvii, 102; Jour. Exper. Med., 1911, xiv, 99, 1912, xv, 90.

The Treponema pallidum has been found in condylomata and in the primary macules, papules, and pustules, as well as in the internal organs, in the lymph-nodes of involved regions, in the spleen, adrenals, and liver, and in the blood.

The organism has been found also in the secondary lesions of syphilis, even at a late period, and in tertiary lesions and in the brain in paresis. It also occurs, sometimes in large numbers, in the lesions of the skin and in the internal organs of the victims of congenital syphilis.

It has been found possible by inoculating monkeys and rabbits, the latter preferably in the testicle, with human syphilitic material, to obtain characteristic lesions containing the treponema, and also to induce similar lesions with pure cultures obtained directly from human tissues. The blood of infected monkeys also gives the Wassermann reaction. There is, therefore, no longer any doubt that the organism is the inciting agent of syphilis. Its exact classificatory relationships are as yet a matter of discussion, but it is generally regarded as a special order of the protozoa.[1]

Fig. 171.—Treponema Pallidum.

(Spirochæta pallida.) India ink preparation.

The clinical results of infection with the Treponema pallidum have led to the suggestion that a number of strains may be included under the one name. In some cases there has been noted an extremely early involvement of the cerebrospinal nervous system, the organisms from these cases producing similar symptoms when transmitted to other persons. Other strains of the spirochete seem to cause extensive local lesions without any tendency to incite a cerebrospinal syphilis. Slight differences in cultural characteristics and in the type of lesion produced in the testicular substance of rabbits also have been noted; but as yet the results cannot be considered as final.[2]

Communicability.—The infective agent of syphilis is readily and most frequently conveyed in man by direct inoculation with the exudate from some lesion of a victim of the disease. This most frequently occurs during sexual intercourse, but may take place in many other ways, through either direct or indirect transmission of the infective exudate to abraded or wounded surfaces.

Syphilis may also be congenitally transmitted, apparently from either the father or the mother. But the transmission of the infective agent through the placental blood is the more common.

Immunization.—Though many attempts have been made to secure active and passive immunity, none has been successful.

[1] For cultural methods, see *Noguchi*, Jour. Exper. Med., 1912, xv, 90. For a general review with bibliography, see *Sobernheim, G.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, vii, 745; *Doflein*, Lehrbuch d. Protozoenkunde, 3d ed., Jena, 1911; *Levaditi* and *Roché*, La syphilis, Paris, 1909.

[2] *Noguchi*, Jour. Exper. Med., 1912, xv, 201; *Nichols, H. J.*, ibid., 1914, xix, 362.

Demonstration of Treponema Pallidum.

The material is most readily obtained from the primary ulcerated lesions by gently scraping with a platinum loop after a preliminary cleansing of the surface, or from mucous patches by a deep scraping with a sharp spoon. From papules, pustules, and roseolæ one may obtain material by expressing fluid through a superficial incision; from lymph-nodes, by the hypodermic needle.

Living Organisms.—By the use of the arc light and a special condenser for dark field illumination in a fresh preparation, one may see the refractile unstained spiral organisms in rapid motion across the dark field.

Staining.—Smears of the material should be made very thin. After fixation in strong methyl alcohol for ten minutes, the Treponema pallidum can be stained by the Giemsa method or the azure-eosin method of Wood. With the Giemsa method it is well to stain for from twelve to twenty-four hours; with the Wood method a warm preparation can be stained in ten minutes.

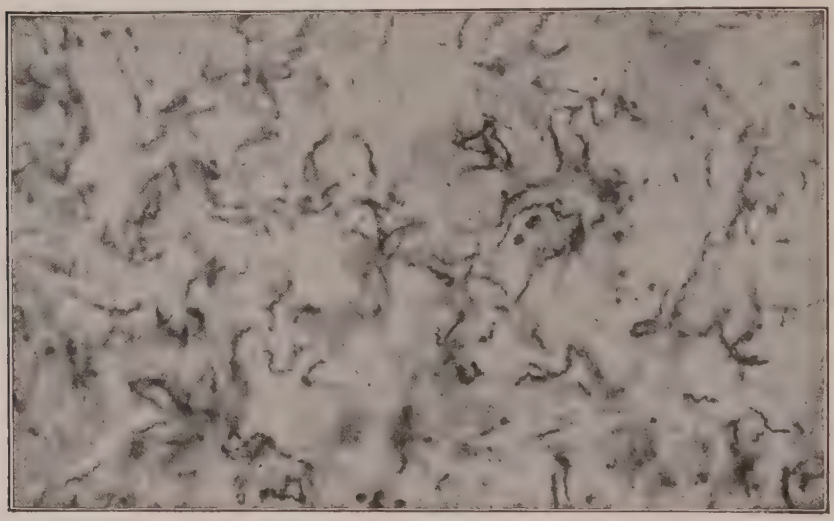


Fig. 172.—Treponema Pallidum.

Stained by the silver method. Preparation of Dr. Noguchi. Showing enormous numbers of spirochetes in the smear of material from syphilitic lesion.

In tissues, the treponema is best demonstrated by the silver impregnation method of Cajal, as modified by Levaditi and others. This is as follows:

1. Fix slices of tissue not over 2 mm. thick in a solution of 1 part (40 per cent.) formaldehyde and 9 parts water, for twenty-four to forty-eight hours.
2. Harden in 96 per cent. alcohol for twenty-four hours.
3. Wash in distilled water until the fragments sink.
4. Impregnate with the following solution:

Pyridin	10 c.c.
Silver nitrate, 1 per cent. aqueous sol.	90 c.c.

Tightly stoppered bottles are maintained at a temperature of 50 to 55° C. in a paraffin oven for five hours.

5. Wash in distilled water and reduce in the following mixture at room temperature:

Pyridin	17 c.c.
Acetone	10 c.c.
Pyrogallic acid, 4 per cent. in dist. water	90 c.c.

The tissue should be kept in the dark and reduction carried out for several hours.

6. Dehydrate in alcohol, embed in paraffin, and cut sections not over 5 micra thick.

If a counterstain is desired, use toluidin blue or Unna's alkaline methylene blue, and differentiate with glycerin-ether.

Noguchi[1] states that in the use of the Levaditi method certain modifications are necessary if satisfactory results are to be obtained. The preliminary fixation of the cerebral tissue in formaldehyde should be very thorough, a period of six months to a year giving the best results. Slices of brain tissue, 5 to 7 mm. thick, are placed in the following mixture:

Formaldehyde, 40 per cent	10 parts
Pyridin	10 parts
Acetone	25 parts
Alcohol	25 parts
Distilled water	30 parts

In this they remain at room temperature for five days. They are then washed in distilled water for twenty-four hours; transferred to 96 per cent. alcohol for three days; washed in distilled water for twenty-four hours; soaked in 1.5 per cent. aqueous solution of silver nitrate for three days at 37° C. or for five days at room temperature; washed in distilled water for two hours; reduced in 4 per cent. pyrogallic solution to which has been added 5 per cent. formalin, for twenty-four to forty-eight hours at room temperature; washed thoroughly in distilled water; transferred to 80 per cent. alcohol for twenty-four hours; then to 95 per cent. alcohol with daily renewals for three days; and absolute alcohol for two days; and embedded in paraffin. Sections should be cut about 3 to 5 micra thick, and should be taken from different portions of the block in order that areas may be obtained in which the neuroglia fibers are not deeply stained and the treponema is black.

By this method the spirals are more or less definitely black, the tissues pale yellow. Double staining reveals the relationships of the organism to the tissue cells.

India Ink Method.[2]—An effective method of demonstrating the syphilis organism in smears is as follows:

The fluid squeezed from a syphilitic lesion on to a slide with as little blood as possible is mixed with a drop of India ink (Chin-Chin waterproof ink manufactured by Günther Wagner), and the mixture spread as in making blood smears. After drying, which is almost immediate, the specimen, examined directly with an oil immersion lens shows the organism, if present, as unstained in a black field (see Fig. 171).

WASSERMANN'S TEST IN THE DIAGNOSIS OF SYPHILIS.

General Considerations.—The principles on which this test is based have been considered on page 220 under the heading *Fixation of Complement.* We have there seen that when a substance capable of inciting the body-cells to the formation of antibodies, *i.e.*, an antigen, is mixed with its corresponding heated serum, *i.e.*, antibody or amboceptor, in the presence of complement, the latter is so "fixed" in combination with the antigen that it is no longer free to enter into any other combination. This is shown by the fact that if such a mixture be placed in contact with the sensitized red blood-cells, no hemolysis is produced.

If, in the above reaction, the heated serum contained no antibody, the complement would not be fixed and hemolysis would take place on the addition of the sensitized red blood-cells.

In this way one may determine the presence in given fluids of specific antibodies, on the one hand, or of antigens on the other, if he have at hand the homologous antigens or antibodies as the case may be. For antigens one may use bacteria or bacterial extracts.

In Wassermann's test[3] it was assumed that syphilitic organs might contain uncom-

[1] *Noguchi*, München. med. Wchnschr., 1913, lx, 737.
[2] *Burri*, Das Tuscheverfahren, Jena. 1909.
[3] *Wassermann, Neisser*, and *Bruck*, Deutsch. med. Wchnschr., 1906, xxxii, 745.

bined portions or products of Treponema pallidum, *i.e.*, free syphilitic antigens, and thus extracts of organs—spleen, liver, etc.—of a syphilitic fetus were made in salt solution or alcohol. But it was discovered later that specific antigens are not necessary for the reaction; that extracts of normal organs—liver, spleen, heart, human or animal —or lecithin in solution can act as antigens in the tests.

Recent work has shown that the concept that there is a specific antigen-antibody reaction in syphilis must be abandoned. The phenomenon is due to some as yet unknown substance produced in the serum of the syphilitic patients, by the reaction between the organism and the body. Extracts of cultures of the Treponema and emulsions from the testes of infected rabbits do not furnish an antigen for the Wassermann test as ordinarily performed.[1]

The reaction may be obtained not only from the blood but also from the spinal fluid, and in the latter, in cases of cerebrospinal syphilis, may be positive when negative in the blood. It is obtained in blood taken post-mortem in some 90 per cent. of those with syphilitic lesions.[2]

The frequency of syphilis in the general population may be inferred from the fact that 15 per cent. of the patients admitted to the Peter Bent Brigham Hospital, and 25 per cent. of those admitted to Bellevue Hospital, give the reaction.[3]

The details of the test cannot be given here. Many types of antigen are employed by different workers and there is as yet no final agreement as to the method. The student is referred, therefore, to special texts for the minute precautions necessary to obtain reliable results.[4]

Luetin Test.

Cultures of Treponema pallidum are ground in a mortar, sterilized by heat, and suitably diluted, and 0.5 per cent. of tricresol are added. From the solution, cultures are made for ordinary bacteria, and rabbit inoculations are carried out so as to determine that no spirochetes have survived the sterilization. The skin is cleansed with alcohol and the luetin is injected intradermally. In the majority of normal persons a very small erythematous area appears after twenty-four hours; in those who have been infected with syphilis a large reddish papule, 5 to 10 mm. in diameter, appears in twenty-four to forty-eight hours, gradually fading toward the end of a week. In more active reactions a pustule may form. The reaction is generally negative in the untreated primary and secondary stages; in tertiary syphilis it is from 80 to 100 per cent. positive. In congenital syphilis the results vary within wide limits. The test is frequently positive when the Wassermann reaction is negative, especially so in cases of late syphilis after treatment where the blood and even the spinal fluid are negative.

Colloidal Gold Reaction.

Another test of great value in cerebrospinal syphilis is a purely physical phenomenon obtained by mixing spinal fluid in varying dilutions with a colloidal gold solution. Various color changes appear in the mixture, which when properly checked give valuable differential diagnostic hints in tabes, paresis, and cerebrospinal syphilis.[5]

[1] *Noguchi*, Jour. Am. Med. Assn., 1912, lviii, 1163; *Craig, C. F.*, and *Nichols, H. J.*, Jour. Exper. Med., 1912, xvi, 336.

[2] *Graves, S.*, Jour. Immunol., 1916, ii, 53.

[3] *Walker* and *Haller*, Jour. Am. Med. Assn., 1916, lxvi, 488.

[4] *Wood, F. C.*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917; *Kolmer, J. A.*, Infection, Immunity, and Specific Therapy, 2d ed., Philadelphia, 1917; *Noguchi*, Serum Diagnosis of Syphilis, 3d ed., Philadelphia, 1912 and *Craig, C. F.*, The Wassermann Test, St. Louis, 1918.

[5] For details of the technique of the test, see *Kolmer, J. A.*, Infection, Immunity and Specific Therapy, 2d ed., Philadelphia, 1917. For method of preparation of the colloidal gold solution, see *Lee, O. I.*, Am. Jour. Med. Sc., 1918, clv, 404. For a discussion of the nature and interpretation of the reaction, see *Vogel, K. M.*, Arch. Int. Med., 1918, xxii, 496.

Rhinoscleroma.

This disease, which occurs especially in eastern Europe and occasionally in other parts of the world, is a chronic inflammation of the nasal, pharyngeal, and laryngeal mucous membrane. In this inflammation a diffuse or nodular formation of new tissue somewhat resembling granulation tissue, occurs, which tends to assume a dense cicatricial character. (Fig. 173.)

A bacillus called *Bacillus rhinoscleromatis* is often found in the lesion. In most of its morphological and biological characters it closely resembles the pneumobacillus of Friedländer (B. mucosus capsulatus), growing

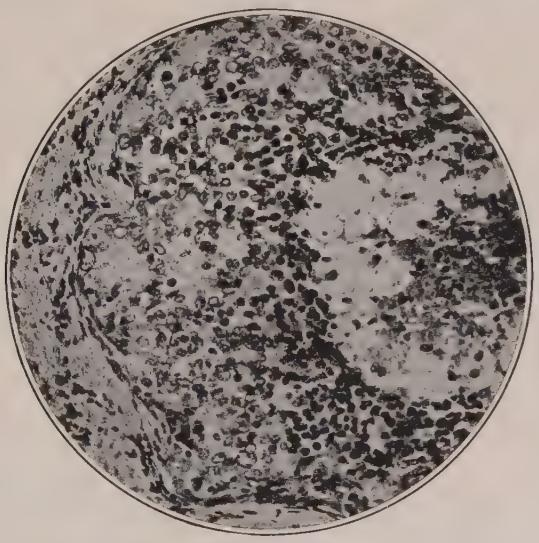


Fig. 173.—Rhinoscleroma Showing Large Clear Cells of Mikulicz, Filled with Bacteria Not Showing in the Photograph.

readily on the common culture media and developing a capsule, and it may be identical with it. The relationship of this bacillus to the lesions of rhinoscleroma does not appear to be as yet definitely established, since inoculations in men and animals have not given positive results.[1]

DIPHTHERIA.

Diphtheria is an acute infectious disease incited by the *Bacillus diphtheriæ* (Loeffler), and usually characterized by a pseudomembranous inflammation on some of the mucous membranes or occasionally on the surface of wounds, and by immediate or remote effects of absorbed toxic substances. The mucous membranes which are the most frequently affected in diphtheria are those of the tonsils, pharynx, soft palate, nares, larynx, and trachea; less frequently those of the mouth, gums, conjunctiva, esophagus, and stomach.

[1] See *Babes, V.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 1237.

Morphology of the Lesions.

The local lesions in mucous membranes may present various phases. Thus there may be a simple redness of the affected surfaces which leaves no trace after death. On the other hand, in the more marked forms of the lesion there may be a fibrinous exudate which infiltrates the mucous membrane, or, intermingled with pus cells, epithelial cells, red blood-cells, bacteria, and granular material, forms a thick or thin pellicle on the affected surfaces (Fig. 131, page 248). This pellicle may undergo coagulation necrosis (Fig. 174), and with this there may be superficial or deep necrosis of the mucous membrane. The false membrane in diphtheria is thus formed by a combination of inflammatory products and necrotic tissue, the extent of the necrosis and the amount of inflammatory products varying in different cases. The membrane may disintegrate or exfoliate, with or without loss of tissue in the underlying mucous membrane. Phlegmon, abscess, and edema are liable to occur as local complications.

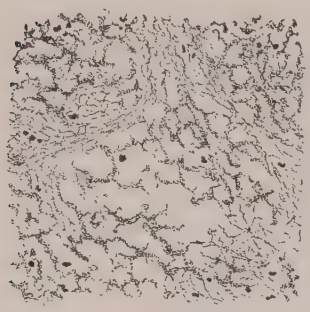


Fig. 174.—Fibrin in Diphtheritic Membrane undergoing Coagulation Necrosis.

Adjacent and distant lymph-nodes are apt to be swollen, and often show, on microscopical examination, endothelial-cell hyperplasia with small foci of cell necrosis and disintegration.[1] Similar foci of cell hyperplasia with necrosis, small spheroidal-cell accumulation and fatty degeneration may be found in the kidney, spleen, and liver. Albuminous degeneration in the kidney, and acute nephritis are not infrequent. Small hemorrhagic foci may be present in the liver and kidneys. Degeneration of the heart muscle may occur.[2] The exact nature of the nerve lesions which may be associated with the late paralyses of diphthera is not yet clear, but degeneration of the peripheral nerves and

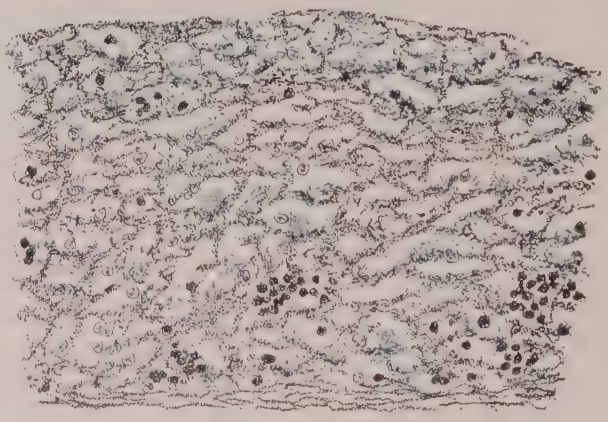


Fig. 175.—Diphtheritic Inflammation of the Tonsil. Showing Loeffler's bacilli in the pseudomembrane.

[1] Consult *Waschkewitsch, T.*, Virchows Arch., 1900, clix, 137.

[2] For studies of the lesions of the myocardium in diphtheria, consult *Scagliosi, G.*, Virchows Arch., 1896, cxlvi, 115; also *Thomas* and *Hibbard*, Boston City Hosp. Rep., 1900, p. 204 (bibl.); for a study of nerve lesions with bibl. see *Batten*, Pediatrics, 1899, vii, 97; also *Rainy, H.*, Jour. Path. and Bacteriol., 1900, vi, 435. For a comprehensive study of the bacteriology and pathology of two hundred and twenty fatal cases of diphtheria, see *Councilman, Mallory*, and *Pearce*, Jour. Boston Soc. Med. Sc., 1900, v, 139.

chromatolysis of the ganglion cells occur, indicating the action of an absorbed toxic substance in the body fluids. Leucocytosis may be present.

Catarrhal bronchitis and bronchopneumonia or simple lobular pneumonia frequently complicate diphtheritic lesions of the upper air passages and fauces.

Bacteriology of the Disease.

Although bacteria of various forms are commonly present in the false membrane, and some of them penetrate deeply into the underlying tissue, the primary and specific excitant of this disease is the Bacillus diphtheriæ of Loeffler.

In man the diphtheria bacilli are largely confined to the seat of local lesion, and sometimes occur here in enormous numbers, especially in the older layers of the pseudomembrane (see Fig. 175). But they may become widely distributed through the body. This appears to be especially the case when the pyogenic cocci are associated with the diphtheria bacillus at the seat of local lesion. The systemic effects in diphtheria appear to be largely due to the absorption into the body of toxic material elaborated locally by the germs. Septicemia or acute visceral inflammations, particularly of the kidney, may occur without evidence of an external local lesion or of the portal of entry of the bacillus.[1]

Concurrent Infections.

The very frequent association of the pyogenic cocci and other bacteria with the diphtheria bacillus gives rise to a series of changes which make the clinical picture and the lesions of diphtheria sometimes very complex. Thus the complicating bronchitis and bronchopneumonia, as well as pyemic symptoms and lesions, may be due to the diphtheria bacillus alone. But these secondary lesions may be due to the presence in the pseudomembrane, and the entrance into the deeper air passages and the blood, of Streptococcus pyogenes, Staphylococcus pyogenes, Diplococcus lanceolatus, Bacillus coli communis, and other bacteria, or of these together with the diphtheria bacillus.[2] Diphtheria bacilli are frequently found also in the exudate from the throats of children with scarlet fever.

Characters of the B. diphtheriæ

This organism, first described and definitely associated with this disease by Loeffler, is a slender rod, in general about 3 μ long, but sometimes shorter and sometimes growing into threads. It occasionally grows in branching forms,[3] and is characterized

[1] For a résumé and bibliography of studies relating to diphtheritic septicemia, see *Braun* and *Thiry*, Gaz. d. hôp., 1899, xx[1], 668.

[2] For a study of the presence and action of the diphtheria bacilli in the lungs, see *Flexner* and *Anderson*, Bull. Johns Hopkins Hosp., 1898, ix, 72.

For a summary of the association of diphtheria and tuberculosis, see *Councilman*, *Mallory*, and *Pearce*, Jour. Boston Soc. Med. Sc., 1900, v, 139.

[3] The branching forms which are occasionally observed in the diphtheria as well as in the tubercle bacillus, together with certain other characters, have led some observers to the belief that these organisms are related to streptothrix and to the moulds rather than to the bacteria. But, for the present at least, it seems wiser to consider them in their more generally acknowledged relationships.

morphologically by marked irregularities in its shape (Fig. 176). While the typical form is that of a round-end, straight, or slightly curved bacillus, it is very apt—perhaps as a result of degeneration—to appear club-shaped or pointed at the ends, and irregularly segmented, and to develop at the ends or elsewhere a strongly refractile material which stains more deeply than the rest of the protoplasm.

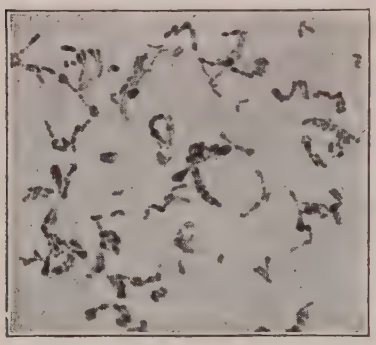


Fig. 176.—B. Diphtheriæ. X 1000.

The diphtheria bacillus is immobile, asporogenous, grows best at blood heat, and thrives on most of the artificial culture media.

In fluids it may be killed by an exposure of ten minutes to a temperature of 58° C.; or of one minute to boiling, but it may remain alive for weeks, or even months, in fragments of dried membrane. It may be stained with Loeffler's alkaline methylene-blue solution or by Gram's method.

It is subject to extreme variations in virulence, forms occurring which with all the usual cultural characteristics are not at all virulent.[1] It is, therefore, often necessary to inoculate suitable animals, the guinea-pig being the best, in order to determine the degree of virulence in organisms of characteristic morphology, especially those derived from chronic carriers.

Action of the Bacillus in Animals.

Inoculations of virulent cultures subcutaneously in guinea-pigs are followed by a localized hemorrhagic edema with a variable amount of whitish exudate. Death usually occurs in from two to five days. In addition to the local lesions there may be —but this is not constant—swelling of the adjacent and of the abdominal lymph-nodes, serous effusions into the pericardial, pleural, and peritoneal sacs, swollen spleen, albuminous and fatty degeneration in the liver, kidney, and, heart muscle, congestion and sometimes hemorrhage of the suprarenals. Microscopical examination shows, in a considerable proportion of cases, fragmentation of nuclei and other evidences of cell death at the seat of inoculation and in the viscera, as well as chromatolysis of ganglion cells in the anterior horn. Animals which survive the inoculations may later develop paralysis, and a similar result may follow the injection into rabbits of culture fluids. The bacilli do not usually gain access to the body at large, but may be found at the seat of inoculation. Inoculation into the mucous membranes of rabbits, pigeons, and certain other animals may result in the development of a pseudomembrane somewhat resembling that of the disease in man.

Diphtheria Toxin and Antitoxin and Diagnosis.

In its growth under artificial culture some strains of the diphtheria bacillus develop and set free in the culture media toxic substances whose chemical composition is as yet unknown. It is this toxic material which is used in the production of diphtheria antitoxin (see page 196).

Communicability.—While the possibility of the transmission of the diphtheria bacillus by domestic animals to man cannot be doubted, the usual source of infective material is the exudates of victims of the disease; virulent bacilli may be conveyed from the mouths of healthy persons to those disposed to the infection. Infection may take place directly by contact, or by coughing and sneezing, or through contaminated

[1] For a study of varieties of the B. diphtheriæ, see *Williams, A. W.*, Jour. Med. Research, 1902, N. S. iii, 83; and *Kolmer*, Jour. Infect. Dis., 1912, xi, 56. See also for full summary of studies on the diphtheria bacillus and its toxins, *Neisser* and *Gins*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, v, 931.

clothing, bedding, or various utensils, or through "carriers."[1] The susceptibility to diphtheria is greatest in the young.

It is important from the prophylactic standpoint to remember that the Bacillus diphtheriæ may remain alive in the mouth of the human subject for many weeks after recovery from the local lesions of the disease, and also that healthy persons when the disease is prevalent may harbor the virulent bacilli in their mouths.

Schick Test.—In the control of epidemics of diphtheria it is important to separate those persons who have a natural immunity from those who are susceptible, in order that the former may be spared the administration of antitoxin. Schick[2] has devised a test which consists in the injection of one-fiftieth of a minimal lethal dose of diphtheria toxin into the skin. The skin is first cleansed with alcohol, and the injection is made with an extremely fine needle. If one-thirtieth of a unit of antitoxin is present in the blood of the person injected, no reaction follows. If there is no antitoxin present, a small area of redness and edema appears in twenty-four to forty-eight hours. The reaction is very reliable.[3] The results of the test show that some 20 to 30 per cent. of children between the ages of two and sixteen give a positive reaction and are probably susceptible to diphtheria. Children under one year of age gave about 85 per cent. of negatives. In adults over 50 per cent. gave negative results. Diphtheria carriers also give negative results.[4] The reaction is of value also in the diagnosis of nasal diphtheria when the membrane is invisible and in differentiating doubtful throat membranes.

Other Bacteria of the Diphtheria-Bacillus Group.

While the diphtheria bacillus varies greatly in the physiological capacities which determine its virulence, its general morphological and cultural characteristics are fairly constant. There are, however, non-virulent bacilli occurring on mucous membranes under normal as well as abnormal conditions which considerably resemble this, but which differ somewhat in both morphological and biological characters from the true diphtheria bacillus and its variants. Such organisms have been called *pseudodiphtheria bacilli* (Bacillus hoffmanni). These non-virulent forms may be regarded as attenuated varieties of the diphtheria bacillus.[5]

The so-called *Xerosis bacillus*, a saprophyte which has been repeatedly found in xerosis conjunctivæ, is apparently a non-pathogenic member of the diphtheria-bacillus group.[6]

TETANUS. (Lockjaw.)

This disease, which is especially marked clinically by muscular spasm, is due to infection by the *Bacillus* or *Clostridium tetani*, an organism often present in the intestinal tracts of horses, cattle, and man. The bacillus is rather widespread and in some places very abundant, occurring with other germs in the soil, especially in manured soil, and gaining entrance to the body through wounds, which are often very slight. The soil in certain regions appears to harbor the tetanus organisms or its spores in especial abundance. Thus in certain districts on Long Island and in New Jersey slight injuries are frequently followed by tetanus. The liability to infection from the spores is greatly enhanced by their association with other organisms or with dirt, splinters, etc., in

[1] For a study of diphtheria carriers, see *Page, H.*, Arch. Int. Med., 1911, vii, 16; and *Chapin*, Sources and Modes of Infection, New York, 2d ed., 1912.

[2] *Schick*, München. med. Wchnschr., 1913, lx, 2608.

[3] *Park* and *Zingher*, Am. Jour. Pub. Health, 1916, vi, 431; *Zingher*, Am. Jour. Dis. Child., 1916, xi, 269; 1917, xiii, 247; *Park, W. H.*, Amer. Jour. Dis. Child., 1921, xxii, 1.

[4] *Weaver* and *Rappaport*, Jour. Am. Med. Assn., 1916, lxvi, 148.

[5] For a study of virulent "pseudodiphtheria" bacilli, see *Hamilton* and *Horton*, Jour. Infect. Dis., 1906, ii, 128.

[6] *Graham-Smith*, Jour. Hyg., 1904, iv, 306. See, also, *Axenfeld*, Augenheilkunde, Jena, 1915.

the wound. It is of practical importance to remember that gelatin and catgut (made from sheep intestine) both may contain tetanus spores. Lack of knowledge of this fact has led to a number of deaths following the injection of solutions of gelatin to check hemorrhage.

The Lesions of the Disease.

The local lesion in tetanus is usually slight and not characteristic, often consisting only in a slight suppuration.

The morphology of the lesions of the nervous system to the existence of which the symptoms of tetanus so directly point is yet obscure. Overfilling of the blood-vessels, cellular exudate into the perivascular spaces, chromatolysis of the ganglion cells of the spinal cord are common. The bacillus remains for the most part at the seat of local lesion and induces its effects by the elaboration of most intense poisons or toxins, called *tetanotoxins*. The action of this toxic substance appears sometimes to continue in the body after the death of the organisms which have elaborated it. This infectious disease affords a most typical example of toxemia.

Characters of the Bacillus Tetani.

It is 2 to 5 μ long, slender, and motile, often growing in pairs or threads and prone to develop a spore in one end (Fig. 177), in which condition the bacillus is larger at this end, being club- or racket-shaped. It is readily stained. At room temperature it grows on artificial culture media, and is strictly anaerobic, flourishing in an atmosphere of hydrogen, but may be artificially adapted to other conditions.

Fig. 177.—Bacillus Tetani. From a culture; showing club-shaped ends with spores.

Some eight types of the organism are recognized[1] but commercial antitoxin seems to be equally effective in neutralizing the toxin of all strains.

The carrier state is readily established in guinea pigs and after about six months the blood shows some antitoxin for the specific type, but the amount of this antitoxin is no index of the degree of resistance. In China 25 per cent. of the human population carry group V in the feces, in California the carrier percentage is the same but group I is most frequent.[2]

The carrier state either in man or animals causes no ill effects but does not give immunity even to the type carried but there is some evidence that recovery under suitable treatment is more probable in carriers.

The spores of the tetanus bacillus are very resistant to drying, to heat, and to various chemical disinfectants.

Characteristic tetanic symptoms followed by death may be induced in mice, guinea-pigs, and rabbits by subcutaneous inoculation of cultures. Man and the horse are markedly susceptible to tetanus; birds are, as a rule, insusceptible, requiring 360,000 times more toxin per kilo of body weight than the horse, for example. If the tetanus bacillus be grown in nutrient broth at blood heat out of contact with oxygen the toxin is developed and mingles with the fluid. This toxin when freed from living germs is capable of inducing the symptoms of the disease. Broth cultures may, after some weeks, have acquired such an extreme intensity that the dried poisonous material, separated from the inert fluids and partially purified, may be fatal to a mouse weighing 15 gm. in a dose of 0.00000005 gm. Estimating according to the relative

[1] *Coleman* and *Meyer*, J. Inf. Dis., 1926, xxxix, 328.
[2] *Bauer* and *Meyer*, J. Inf. Dis., 1926, xxxviii, 295.

weights of the subjects, the minimal fatal human dose would be about 0.00023 gm. This toxin is rendered inert by a temperature about 65° C. and by light.

Tetanus Antitoxin.

By procedures similar to those described in diphtheria immunization (page 196), the tetanus toxin has been used to secure artificial immunity in dogs, goats, and horses, and here also the blood serum of the immunized animals has been prepared and employed in man for therapeutic purposes with some degree of success.[1]

The tetanus toxin induces its effects in the body chiefly by its action on the central nervous system. It has been shown to reach the nerve centers from the seat of growth of the bacillus, by way of the axis-cylinders of the motor nerves. The tetanus antitoxin, on the other hand, which may be injected for protective purposes, is not taken up by the nerves, but passes into the blood- and lymph-vessels and tissue fluids. The power of the antitoxin to neutralize toxin is apparently limited to that portion of the latter which has not been absorbed by the nerves, but is still free either at the seat of production or in the blood or lymph.

The theoretical promise of the tetanus antitoxin for therapeutic purposes in man is thus in practice rendered in a large measure futile, because the existence of the disease is not recognizable until the toxemia is sufficiently marked to produce the nervous symptoms, at which time, union of the toxin with the nerve tissues having been effected, the usefulness of the antitoxin is limited to the neutralization of the unabsorbed toxin. Statistics are as yet too meager to justify a final question as to the practical value of tetanus serum therapy, but cures have been obtained even after nerve symptoms have begun when the serum is introduced by intraspinous injection in large amounts. Splendid results have followed prophylactic injections.

MALTA FEVER.

This disease, which has been most frequently observed along the shores of the Mediterranean and in India, and occurs in South America and the West Indies, is characterized by prolonged pyrexia with irregular remissions. In the rather rare fatal cases there may be considerable enlargement of the spleen, and albuminous degeneration in the liver and kidneys. Acute nephritis may occur.

In the spleen in this disease there are constantly present short bacilli sometimes assuming coccoid forms, which are negative to Gram and are readily cultivated on artificial media. Inoculations of cultures into monkeys and other animals have proved the biological relation of the organism *Brucella melitensis* to the undulant fever first studied in Malta. The source of the organism there has been shown to be goats' milk, ten per cent. of the samples of which have been found to be contaminated with the organism. An almost identical organism, *Brucella abortus*, has

[1] For the results of treatment of tetanus see *Ashhurst, A. P. C.*, Jour. Am. Med. Assn., 1926, lxxxvii, 2089; also *Park* and *Williams*, Pathogenic Microorganisms, 8th ed., Philadelphia, 1924.

been frequently demonstrated in cows' milk and it has been shown that in the United States[1] a number of persons suffering from an irregular type of fever give high blood agglutinations to *Brucella abortus* and in some instances the bacillus has been isolated from the circulation.

BUBONIC PLAGUE. (Oriental Plague; Black Death.)

Types of the Disease.—This disease presents three main types—the bubonic, the pulmonary, and the septicemic.

The most common is the *bubonic*, which is characterized by an intense inflammatory hyperplasia of the lymph-nodes, most frequently the inguinal or axillary. The surrounding tissue may be involved; hemorrhage, necrosis, or suppuration in the nodes may occur. Coincident with these local reactions there may be albuminous degeneration, focal necrosis, and leucocytosis from toxemia, or secondary foci of inflammation in the spleen or lungs or liver. A second type of the infection is the *pulmonary*, in which larger or smaller areas of the lungs are involved in bronchopneumonia with associated secondary involvement of the bronchial lymph-nodes. In the *septicemic* type of bubonic plague there may be a general involvement of the lymph-nodes and -nodules of the body with the marks of toxemia, without an indication of the point of primary infection.

In all these various phases of the disease the plague bacillus may be present often in enormous numbers in the primary buboes and in the secondary lesions and in the viscera; in the consolidated areas and in the sputum in the pulmonary type, and, in the septicemic type, in the blood. An attack confers immunity.

Characters of the Bacillus Pestis.

The plague bacillus was discovered in 1894 by Kitasato and Yersin, and its rôle as the excitant of the disease was soon established. It is a short, thick, motile, round-end bacillus, often staining more deeply at the ends than in the middle. It sometimes grows in chains and may be capsulated, not forming spores; it is decolorized by Gram's method. It grows readily though not voluminously on the ordinary culture media at blood heat.[2] This organism is killed by drying for a few days and by exposure to sunlight for a few hours. Subcutaneous inoculations into guinea-pigs and rabbits is followed by local hemorrhagic and serous inflammation with typical involvement of the regional lymph-nodes and by septicemia. Death may follow in from one to five or six days, with albuminous degeneration of the viscera, hyperplasia of the spleen, and petechial hemorrhages.

Portals of Entry.—The chief portals of entry in man are abrasions or wounds of the skin, the lungs, and the intestines. The spread of the infectious material in overcrowded and unsanitary districts readily takes place by rats, which are very susceptible to the disease and may be infected by feeding.[3] Through mosquitoes, flies, and other vermin,

[1] *Hull* and *Black*, Jour. Am. Med. Assn., 1927, lxxxviii, 463 (bibl.).

[2] See *Dieudonné* and *Otto*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 155.

[3] The ground squirrels along the Pacific Coast were widely infected with plague bacilli and were a menace to the population of that region; see Pub. Health Repts., U. S. Mar. Hosp. Serv., 1910, xxv, 27.

also, the bacilli may be conveyed from man to man or from dead rats or their dejecta to man;[1] but the most important vector is the rat flea, which has been definitely proved to be the most usual agent.

Preventive Inoculation has been largely practised in the East by the Haffkine method. This consists in the subcutaneous injection of beef-tea cultures of the plague bacillus, which have been killed by heating. Moderate local inflammatory reaction and slight fever may follow the injection. The statistics seem to indicate that among exposed persons the mortality may be considerably reduced by this preventive inoculation.[2]

An antiplague serum, prepared by the immunization of horses, has been used by Yersin with at least promising results.[3]

HEMORRHAGIC SEPTICEMIA.

Many of the lower animals are victims of acute infections, septicemic in character, often with petechial hemorrhages in the viscera and serous membranes and marked intestinal disturbances. These are called *hemorrhagic septicemias.*

Associated with these and doubtless their inciting agents are several bacilli which may be classed, as is done by Hueppe, Kruse, and others, with the plague bacillus under the designation, *the hemorrhagic-septicemia group.* These are mostly small, short, sporeless forms growing readily on the ordinary media as facultative anaerobes, not fluidifying gelatin, and decolorizing by Gram. Some of these are motile, others not. Among these may be mentioned the bacillus of mouse typhus (*B. typhi murium*), the bacillus of chicken cholera (*B. choleræ gallinarum*), the bacillus of swine plague (*B. suisepticus*). Several species related to these and to the plague bacillus are pathogenic in man; thus the *B. hæmorrhagicus septicus* of Babes, the *B. hæmorrhagicus* of Kolb, the *B. hæmorrhagicus velenosus* of Tizzoni and Giovanni.

The recognition of these and related species may be of especial significance in connection with the diagnosis of bubonic plague by cultures and animal inoculations.[4]

Bacillus Aërogenes Capsulatus (Bacillus Welchii, Gas Bacillus, Bacillus Perfringens).

This bacillus was described in 1891–92 by Welch and Nuttall. Later studies of Welch and Flexner and many others have confirmed the original belief that the bacillus is a frequent excitant in man of a serious infectious disease, characterized by a local widespread serous and emphysematous phlegmonous inflammation, frequently associated with gangrene and general symptoms of a profound toxemia.

The Bacillus aërogenes is rather large, on certain media is spore-forming, is often encapsulated, and occasionally forms chains. It retains the stain by Gram's method. It is anaerobic, growing readily in a variety of artificial culture media.

Rabbits are not susceptible to even large intravenous injections of pure cultures. But if the animals be killed soon after inoculation, within a few hours, at room temperatures, an abundant development of gas

[1] On insects as plague-carriers, see *Herzog*, Am. Jour. Med. Sc., 1905, cxxix, 504.

[2] For summary of results of the Haffkine method, see *Forsyth*, Lancet, 1903, ii, 1646; also *Slaughter*, Bull. Johns Hopkins Hosp., 1903, xiv, 307.

[3] See, for critical summary and bibl., *Netter*, Arch. de méd. expér., 1900, xii, 86.

[4] For studies on various forms of hemorrhagic infection, see *Babes*, Verhandl. d. deutsch. path. Gesellsch., 1900, ii, 262; also *Hutyra*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, vi, 64

occurs throughout the body. On the other hand, the subcutaneous injection of a very small quantity of the fresh edematous exudate is followed by the typical local and general marks of infection. Guinea-pigs are more susceptible than rabbits to inoculation, either with cultures or fresh material, and develop characteristic lesions.

While infection may occur without gas, there is an abundant formation of gas in the tissues after death. This is largely hydrogen formed through the splitting by the bacillus of either sugar or proteins. While the gas may be present in any of the tissues, in the body cavities, and in the blood-vessels, it is especially in the liver after death that the marks of its accumulation are most striking. This organ may be riddled with small holes, presenting an appearance which has been characterized as "foamy liver" (Fig. 549, page 851). Crushing wounds of the extremities are often followed by gas gangrene, the bacteria developing in the necrotic tissues and spreading along the muscle bundles. The gas formed in the dead tissue causes further destruction, through stoppage of the capillary circulation either by gas emboli or by pressure, being retained by the fascial planes of the muscle. Free incision of the muscle to relieve pressure is the only means of preventing further extension.

Infection may occur through wounds or injuries in any part of the body. It has been frequently observed in pregnant and puerperal women.[1] Ulcers of the stomach and intestine or of the urinary tract may be portals of entry. One of the more common forms of local infection is the so-called gaseous phlegmon or emphysematous gangrene. Pulmonary and pleural lesions, appendicitis, and peritonitis are described, as well as gaseous abscesses and purulent meningitis. While the usual action upon the tissues is the induction of bloody edema and necrosis, this bacillus is also occasionally pyogenic.

The Welch bacillus produces at least two distinct toxins, one hemolytic, causing diffuse staining of the tissues, the other purely toxic. An antiserum has been produced by Weinberg, and has proved of great value in infections with this organism.[2]

The natural habitats of the organism are the soil and the intestinal canal. This accounts for the relative frequency of infection through the intestinal and genitourinary tracts and through wounds contaminated with dirt.

Infection, especially from the intestinal canal, may occur apparently during the later hours of life, with or without symptoms and with a post-mortem formation of gas. It is often difficult to determine, since gas formation occurs so early and so extensively after death, whether the entrance has or has not been effected during life. Usually, however, when the autopsy is done immediately after death, no mechanical lesions due to gas are found in the organs. It seems fair to infer, as the result of animal experiments, that when the gas formation, even after death, is widespread, ante-mortem infection has occurred.

[1] For a study of B. capsulatus in puerperal infections, see *Little*, Bull. Johns Hopkins Hosp., 1905, xvi, 136.

[2] See *Weinberg, M.*, Compt. rend. Soc. de biol., 1914, lxxvii, 543; and *Weinberg, M.*, and *Séguin, P.*, Compt. rend. Acad. de sc , 1917, clxiv, 365; clxv, 199. *Bull* and *Pritchett*, Jour. Exper. Med., 1917, xxvi, 119.

Concurrent infection with other organisms, especially the pyogenic cocci, the bacillus of malignant edema (*Vibrio septique*), and the Bacillus œdematiens, is frequent.

Welch and Nuttall early called attention to the importance of recognizing the possibility of infection with this bacillus in judging of a certain class of cases of alleged air embolism.

It is probable that the Bacillus aërogenes capsulatus is identical with forms which have been described under various names in connection with cases of gaseous phlegmon, or so-called malignant edema.[1]

Bacillus œdematiens, Bacillus œdematis Maligni

Malignant Edema.[2]

This disease is of occasional occurrence in man and certain domestic animals—horses, cattle, sheep—usually following some form of traumatism. It is a septicemia with local, often hemorrhagic edema, visceral degeneration, etc.

The bacillus of malignant edema, *Bacillus œdematis maligni*, which is frequently present in dust, in putrefying substances, and in soil, considerably resembles the Bacillus aërogenes capsulatus in both its morphological and biological characters. It is, however, more slender, and more apt to form threads; spore formation occurs readily in the ordinary media. It decolorizes partially by Gram's method. Other differential characters are to be made out in cultures. It is an excitant of hemorrhagic edema, but with slight if any development of gas.

Other Bacteria which may Induce Hemorrhagic Septicemia.

Nearly related to the Bacillus aërogenes capsulatus and to the bacillus of malignant edema are several other spore-forming anaerobic bacilli occurring especially in the earth, in excrement, and in various rotting substances. Some of these appear to be of pathogenic significance in the lower animals under both natural and experimental conditions.

Thus the *Quarter-evil* (*Rauschbrand; charbon symptomatique*), especially in Europe, is a serious infectious disease of sheep, goats, and cattle. At the seat of infection, often in the legs, there is a hemorrhagic edema with gas formation, the involved region often becoming much swollen and black in color ("black leg"). The bacillus which is the excitant of this disease is known, and preventive inoculation has been practised.

Howard has described a group of cases of hemorrhagic septicemia characterized by hemorrhages into the skin, serous membranes, and viscera, in which capsulated bacilli apparently related to the above-described bacillus of Friedländer (page 251) have been found.[3]

Meat Poisoning.

Meat poisoning may be due to some strain of *Bacillus enteritidis* which infects various animals. The meat of these diseased animals is not abnormal in appearance or taste but may contain the organism, and if

[1] For an excellent critical résumé of this subject, with bibl., see *Welch*, Bull. Johns Hopkins Hosp., 1900, xi, 185. See also, *Ghon* and *Sachs*, Centralbl. f. Bakteriol., Orig. I, 1904, xxxv, 665; 1904, xxxvi, 1; *Simonds, J. P.*, Studies in Bacillus welchii, Monographs of the Rockefeller Institute, New York, No. 5, 1915; and *Weinverg, M.*, and *Sèguin, P.*, La gangrène gazeuse, Paris, 1918; and *Pease, M. C.*, Proc. Soc. Exper. Biol. and Med., 1919–20, xvii, 30.

[2] *v. Wert, F.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 1912, iv. 837 (bibl.).

[3] *Howard, W. T.*, Jour. Exper. Med., 1899, iv, 149; also *Blumer* and *Laird*, Bull. Johns Hopkins Hosp., 1901, xii, 45. See also Typhus and Rocky Mountain Spotted Fever (p. 333–334).

not thoroughly cooked may induce serious gastrointestinal disorders in man. The meat of diseased cows and calves most frequently has been the source of infection. The infection is most common in summer and the infective agent may apparently be conveyed from man to man through excreta.

Several other forms of meat poisoning, some resembling typhoid fever, others involving a mild or violent gastroenteritis, others especially characterized by toxemic symptoms have been attributed to the presence of various bacterial organisms which we cannot consider further here.[1]

Botulism.

This is a toxemia characterized by chills, giddiness, trembling, headache, and sometimes vomiting, followed by symptoms such as loss of accommodation, dilated pupils, ptosis, aphonia, etc., referable to the action of some toxic substance.[2] Death may follow general motor paralysis and dyspnea, due to the action of the toxin on the cells of the central nervous system. Visceral hyperemia, petechial hemorrhage, and albuminous degenerations may be noted. The disease is due to the toxins formed by the *Bacillus botulinus*, first isolated by van Ermengem from a contaminated ham which had poisoned many persons. The bacillus is a spore-bearing anaerobic organism, which is, however, aerobic when growing in symbiosis with other organisms such as Sarcina or Bacillus subtilis.

It is believed that the toxins inducing botulism are formed in the contaminated food—ham, sausages, and canned meat and vegetables[3]—before their ingestion, but as the poison is rapidly destroyed by heat at a temperature above 80° C., it is obvious that only uncooked foods are dangerous.

RELAPSING FEVER. (Typhus Recurrens; Famine Fever; Spirillum Fever; Seven-Day Fever.)

This disease is common in India, Africa, and many tropical countries, and has occurred in Russia and in the United States.[4] It is characterized, apart from the fever and associated symptoms, by the presence in the blood at certain periods of a spiral organism discovered by Obermeier in 1873. Some six closely related species of spirochetes inducing the different forms of the disease have been described, of which the *Spirochæta obermeieri* and the *Spirochæta duttoni* are the best known.

There may be albuminous degeneration in the viscera, leucocytosis, catarrhal or croupous inflammation of the mucous membranes of the respiratory and digestive organs, and ecchymoses in the skin and in the mucous and serous membranes; as well as pneumonia and pleurisy, degeneration of the cardiac muscle, and hyperplasia of the mesenteric lymph-nodes. The *spleen* may be large and flabby, this change being so extreme that rupture has occurred during life; it may also be the seat of infarctions, and these have given rise to peritonitis.

[1] For a brief résumé of this group, see *Hiss* and *Zinsser*, Text-book of Bacteriology, 5th ed., New York, 1922, p. 686, 740.

[2] *van Ermengem*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1912, iv, 909 (bibl.).

[3] *Dickson, E. C.*, Jour. Am. Med. Assn., 1917, lxix, 966; and Botulism, Monograph No. 8, Rockefeller Inst., New York, 1918, and *Dickson, E. C., Burke, G. S.*, and *Wark, E. S.*, Arch. Int. Med., 1919, xxiv, 581.

[4] *Carlisle*, Jour. Infect. Dis., 1906, iii, 233 (bibl.), describes two cases.

Characters of the Spirochæta Obermeieri.

In the blood of all parts of the body during the febrile attacks may be found, in very large numbers, a long, slender spiral called from its discoverer *Spirochæta obermeieri* (*Sp. recurrentis*) (Fig. 178). The organisms disappear from the blood during the afebrile intervals, and it has been shown that at this time they accumulate in the spleen, where they are destroyed in large numbers, apparently through the action of phagocytic cells. The organism is in general from 7 to 9 μ in length, sometimes longer, and performs rapid, undulating movements.

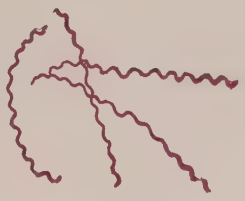


Fig. 178.—Spirochæta Obermeieri.

The inoculation of healthy men and of monkeys with the blood of relapsing-fever patients which contains the organism induces a similar disease. Successful inoculations of white rats have been made with a spirochete believed to be of this species or a closely related one, *Spirochæta novyi*.[1] Pure cultures of these organisms have been obtained through several generations,[2] and for the reasons indicated, and since the organism has never been found except in connection with the disease, there is every reason for believing that the Spirochæta obermeieri is the excitant of relapsing fever.[3] The organisms are considered to be protozoa by many observers, though Novy regards them as definitely bacterial in nature. It is probable that Spirochæta obermeieri is transmitted by lice, especially *Pediculus vestimenti* and *Pediculus capitis*, and possibly also by the bedbug. The spirochetes are not carried directly into the skin by the bites of the insects, but when the lice are crushed, as in scratching, the organisms enter through the abrasion of the skin.[4] When the fingers are contaminated, the infection may be carried to the eyes by rubbing, and may then become general through the conjunctiva.

TICK FEVER.

This is a disease of Uganda, Abyssinia, and the Congo region in Africa. The parasite has been studied by Novy and Knapp,[5] and designated by them Spirochæta duttoni. The pathological changes induced in the body by the parasite are the same as those caused by the presence of the Spirochæta obermeieri. The organism is transferred by the bite of the *Ornithodorus moubata*, a tick in which it can live for a long time. The disease has been induced in monkeys by causing these animals to be bitten by the infested ticks.[6]

Morphologically the parasite resembles very closely the Spirochæta obermeieri, except that it is somewhat thicker.

[1] *Norris*, *Pappenheimer*, and *Flournoy*, Jour. Infect. Dis., 1906, iii, 266.

[2] *Noguchi*, Jour. Exper. Med., 1912, xvi, 199.

[3] See for rèsumè, *Novy* and *Knapp*, Jour. Infect. Dis., 1906, iii, 291; also *Mühlens*, *P.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, vii, 864 (bibl.)

[4] *Nicolle*, *Blaizot*, and *Conseil*, Compt. rend. Acad. d. sc., 1912, cliv, 1636; clv, 481; *Nuttall*, Parasitology, 1912–13, v, 262.

[5] *Novy* and *Knapp*, Jour. Infect. Dis., 1909, iii, 379; *Todd* and *Wolbach*, Jour. Med. Research, 1914, N. S. xxv, 27.

[6] *Dutton* and *Todd*, Brit. Med. Jour., 1905, ii, 1259; *Ross* and *Milne*, Brit. Med. Jour., 1904, ii, 1453.

VINCENT'S ANGINA.[1]

This is an inflammation of the mouth, pharynx, and tonsils, often associated with a pseudomembrane and sometimes leading to ulceration. There is usually but moderate systemic disturbance. While in the lesions there are frequently many bacteria, two forms usually associated are most commonly found, one spindle-shaped resembling a bacillus, the other spiral-shaped, longer than the first, with shallow irregular curves, and staining with difficulty.

These two organisms have been cultivated under anaerobic conditions.[2]

YAWS (FRAMBŒSIA TROPICA).

This disease of tropical and subtropical countries is characterized chiefly by a papular eruption, with ulcerations suggestive of a relationship to syphilis. Castellani in 1905 demonstrated in the lesions spirochetes resembling Treponema pallidum; and his observation has been repeatedly confirmed. The infective agent can be transmitted to monkeys and to rabbits by inoculation of material from the lesions.[3] It seems clear that though the inciting agent of yaws, *Spirochæta pertenuis* (*Treponema pertenue*) resembles the syphilis organism, the diseases are entirely distinct. Salvarsan, however, is therapeutically beneficial.

HYDROPHOBIA. (Rabies.)

Morphology of the Lesions.

This is an infectious disease occurring most frequently in the carnivora, and especially common in dogs and wolves, and usually communicated to man by bites of the rabid animals.

The lesions are not constant nor are they characteristic. Though well marked in some cases, in others they are but very slightly developed. Changes, when present, are apt to be most pronounced in the medulla oblongata and pons, but they may be observed in the spinal cord. They consist of small hemorrhages, of accumulation of leucocytes in the perivascular lymph spaces about the blood-vessels (Fig. 179) and around the ganglion cells, of thrombi in the smaller blood-vessels, and finally of chromatolysis of the ganglion cells.[4]

Changes have been described in the intervertebral ganglia and in the plexiform ganglia of the pneumogastric nerve, which, although not limited to rabies, are yet so frequently present as to be apparently of value in diagnosis. The lesions consist in degeneration or atrophy or destruction of the ganglion cells with a proliferation of the endothelial cells lining the capsule.[5]

[1] *Vincent*, Ann. de l'Inst. Pasteur, 1899, xiii, 606; and Lancet, 1905, i, 1260.

[2] For a study of fusiform bacilli, see *Dick*, Jour. Infect. Dis., 1913, xii, 191; *Krumwiede* and *Pratt*, ibid., 1913, xii, 199; 1913, xiii, 438, and *Larson* and *Barron*, ibid., 1913, xiii, 429. For cultures of spirochetes, see *Noguchi*, Jour. Exper. Med., 1912, xv, 81; ibid., 1912, xvi, 194.

[3] See, for a study of experimental yaws in the monkey and rabbit, *Nichols, H. J.*, Jour. Exper. Med., 1910, xii, 616.

[4] *Bailey, F. R.*, Jour. Exper. Med., 1901, v, 581.

[5] See *Ravenel* and *McCarthy*, University Med. Mag., 1901, xiii, 766.

Animal Inoculations.

Since the infective agent of rabies is present in the central nervous system of victims of the disease, this material, *i.e.*, brain and spinal-cord tissue, especially the latter, is used in experimental work. This is called the "virus" of rabies. Rabbits and guinea-pigs, as well as various other animals, are susceptible to subdural injections of a small amount of emulsion of the infective nerve tissue. After an incubation period varying in different animals, these succumb with characteristic symptoms and lesions.[1]

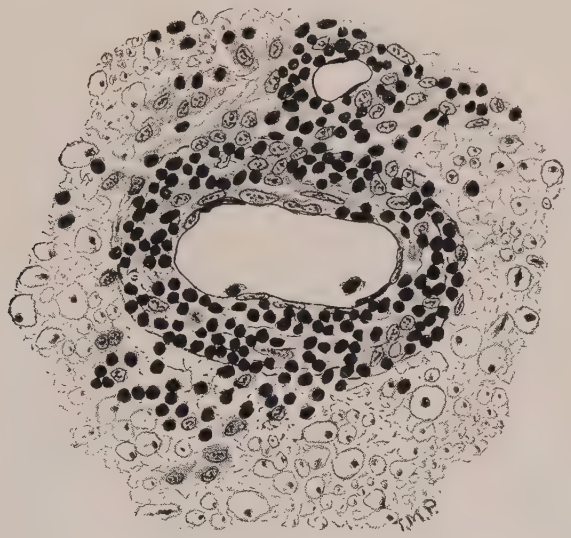


Fig. 179.—Hydrophobia. Transverse Section of Small Blood-vessels in the Spinal Cord. Showing accumulation of leucocytes and proliferation of connective-tissue cells in the adventitia of the vessels.

The Excitant of the Disease.

The infective agent appears to be carried especially along the nerves from the point of inoculation to the central nervous system, where it seems to develop. It is not present in considerable quantity in either blood or lymph.

It is known that the infective agent is in the saliva and salivary glands of rabid animals, and that it may be present in the saliva of the dog from three to five days before the symptoms of the disease appear. It seems to be especially concentrated in the central nervous system. It is readily rendered inert by corrosive sublimate and other germicides. It resists cold even to −20° C. but loses virulence after one hour's exposure to 50° C. It is preserved for some time in glycerin.

[1] For further data, see epitome in *Kolle* and *Hetsch*, Die experimentelle Bakteriologie, 5th ed., Berlin, 1919.

It has been found that the rabic virus may pass the pores of an unglazed porcelain filter not pervious to ordinary bacteria, so that some form or developmental phase of the organism must be extremely minute.

Negri Bodies.—In 1903 Negri announced that he had seen in sections of the central nervous system of rabic animals within the ganglion cells, rounded bodies from 1 μ to 23 μ long, containing vacuoles and granules often grouped around a larger central structure. These bodies he regarded as parasites belonging among the protozoa and believed them to be the specific inciting factors in hydrophobia. These intracellular structures, now called "Negri bodies," have been the object of many careful researches, and the observations of Negri have been in general confirmed and extended.

FIG. 180.—NEGRI BODIES.
In smears from Cornu Ammonis of rabic dog.

The Negri bodies are, as a rule, most abundant in the large ganglion cells of the hippocampus major (Cornu Ammonis), but occur in ganglion cells of the cerebral cortex and elsewhere. They are readily stained and appear to consist of a rounded or oval homogeneous basement substance containing a central body surrounded by variously shaped granules (Fig. 180). They occupy central or peripheral positions in the ganglion cell and vary greatly in number in different cases of rabies.

Similar cell inclusions have been found in animals inoculated with "fixed virus" (see below), but they are smaller and more difficult of detection than in street rabies and in animals inoculated with the street-rabies virus. Negri bodies have been found in nearly all cases of street rabies examined for them, and in no disease other than rabies. Their

constancy in street rabies has led workers in this field to regard them as of the utmost diagnostic value. While their nature is not yet definitely established, their morphology and staining qualities seem to be consistent with the assumption of their protozoan character. They have indeed been named by Williams *Neuroryctes hydrophobiæ*. Their uniform presence in street rabies and the frequent presence of smaller similar structures in fixed virus and in animals inoculated with this, together with their absence in diseases other than rabies, seems to justify the tentative assumption of a specific etiological relationship to hydrophobia.[1]

Preparation and Staining of "Negri Bodies."

Williams-Lowden Method.—While the earlier studies were made on sections, Williams and Lowden have shown that in stained smears of the nerve tissue made upon slides, which is much simpler than sectioning, the "bodies" are more clearly demonstrated, and that this method for diagnostic and other purposes is to be preferred. The technique of making and staining smears as devised by Williams and Lowden is in outline as follows:

On a clean slide a small bit of the gray matter is placed, and a cover-glass is lightly pressed upon it, spreading it into a thin layer; the cover-glass is then moved along the slide, leaving a uniform thin smear of the substance. The smears are dried in the air.

Staining may be done by the Giemsa solution or by the eosin methylene-blue stain of Mallory. The latter is effected as follows:

Fix smears in Zenker's fluid for one-half hour; rinse and place in iodinized, 95 per cent. alcohol for fifteen minutes; in 95 per cent. alcohol and absolute alcohol, successively, one-half hour each; aqueous eosin solution, twenty minutes; rinse in water; place in Unna's alkaline methylene-blue solution (methylene blue, 1; carbonate of potash, 1; water, 100) diluted 1 to 5 or 1 to 10 for fifteen minutes; differentiate in 95 per cent. alcohol from one to five minutes; dry with filter paper; balsam. By this method the cytoplasm of the Negri bodies is magenta in color, the central bodies and associated granules dark blue, the ganglion cell-body light, and its nucleus a darker blue.[2] The red blood cells are a brilliant eosin pink.

Frothingham's Impression Method.—To avoid the distortion of the ganglion cells and the disturbance of their relationships inevitable in the "smear" method, and to enable the operator to recognize the topography and thus select for examination the larger cells lying just outside the hilus in which Negri bodies are more commonly found, the following procedure has been recommended for rapid diagnosis.[3] Dissect out the cornu Ammonis, removing extraneous tissue from the edges. With scissors cut out a small disc at right angles to the long axis of the organ from any part desired and place it upon a board near its edge so that one of the flat surfaces of the disc rests upon the board, the other being exposed. The grouping of nerve cells may now be seen in distinct white lines.

Place a thoroughly cleaned slide upon this disc of tissue, press it gently and lift suddenly. The disc adheres to the wood, and an impression of its upper surface is left upon the glass. Repeat, using a new portion of the slide and a little more pressure. Make a third impression, using still more force, and a fourth, using sufficient pressure to flatten the disc almost completely. Before these impressions have dried, place slide in methyl alcohol for one-half to two minutes or longer. Remove from the alco-

[1] For a résumé and study of "Negri bodies" see *Williams* and *Lowden*, Jour. Infect. Dis., 1906, iii 452 (bibl.); and *Watson, E. N.*, Jour. Exper. Med., 1913, xvii, 29. For the preliminary anncuncement of a study of rabies with a special culture medium in which granular and larger nucleated bodies were found, see *Noguchi*, Jour. Exper. Med., 1913, xviii, 314.

[2] For the details of the Giemsa staining and stain for Negri bodies suggested by Van Gieson, see *Williams* and *Lowden*, Jour. Infect. Dis., 1906, iii, 452, and foot-note p. 461.

[3] See *Frothingham*, Jour. Med. Research, 1905–06, N. S. ix, 471; also Am. Jour. Pub. Hyg., 1908, xviii, 4. For a study of virus freed from cells of host, see *Poor* and *Steinhardt*, Jour. Infect. Dis., 1913, xiii, 263.

hol and cover with Van Gieson stain. Warm gently for one-half to two minutes till a light vapor rises. Wash in water, dry with filter paper, and examine without cover, first with low power to locate best cells, then with an oil immersion.

The stain may be modified by the use of water 20 c.c.; saturated alcoholic solution of fuchsin, 3 drops; saturated aqueous solution of methylene blue, 1 drop, prepared fresh each day. The Negri bodies are stained pale pink to pinkish red, the ganglion cells are bluish.

Preventive Inoculation.

Notwithstanding his total ignorance of the microorganisms concerned in inciting hydrophobia, his genius in wise experiment enabled Pasteur to establish a method which has proved most beneficent for artificial immunization against the disease.

He first obtained a virus of high and definite intensity. This was accomplished by a series of inoculations beneath the dura mater in rabbits of portions of the spinal cords of rabid animals. This was called "*virus fixe*"—fixed virus. It was found that by drying in the air, spinal cords of rabbits having definite and high virulence—fixed virus—with due protection against aerial contamination, the virulence diminished day by day. With virus thus obtained of virulence ranging from that which is practically inert to that of the utmost potency, it has been found possible, by subcutaneous injections, safely to accustom both animals and men to the presence of amounts of hydrophobia virus contained in the spinal cord emulsion, which under ordinary conditions would prove speedily fatal. In other words, it has been found possible to confer artificial immunity against the disease.

This process occupies several weeks, and immunization must be completed before the disease has begun to manifest itself; but as the incubation period in hydrophobia is fortunately a long one—the average is about forty days—it has been possible, in a large and increasing number of cases, to save the lives of persons bitten by rabid animals.[1]

This work is now done in laboratories maintained for the purpose and requires care and experience in the preparation of the virus as well as in diagnosis.

Diagnosis.

In view of the importance of diagnosis in animals which have died or have been killed under suspicion of rabies, the brain, spinal cord, medulla, and ganglia should be saved.

The presence of Negri bodies is believed to be diagnostic for rabies, so that these should be sought for in the fresh tissue by the methods indicated above. But considerable experience is required for this work.

The examination of the plexiform and other ganglia, and of the perivascular tissue and ganglion cells in hardened tissue for possible changes, may be useful in cases of doubt, though not in themselves positively diagnostic. Finally, it may be necessary to have recourse

[1] See, for details of preventive inoculations, *Park* and *Williams*, Pathogenic Microorganisms, 6th ed., New York, 1917, p. 569; also for general summary and bibl. *Stimson*, Bull. 65, Hyg. Lab., Pub. Health Ser., Washington, 1910.

to the biological test, that is, subdural inoculation of susceptible animals with fresh material from the medulla of the suspect. Portions of the fresh medulla in watery emulsion are inoculated beneath the dura mater of three healthy rabbits or guinea-pigs, and the development of rabic paralysis and other symptoms awaited. This operation for diagnostic purposes should be done only by one experienced in this subject.[1]

It is always wise *not* to kill animals suspected of rabies, but to keep them under observation in confinement. Rabies being always fatal, recovery from a suspicious disease excludes it, so that further protective measures may be clearly unnecessary. On the other hand, the carefully observed symptoms of a suspected animal may even in the event of a fatal termination afford valuable evidence. If the laboratory for diagnosis be accessible, it is well, if the suspected animal should die or be killed, to send the whole animal or the head cut off low down, packed in ice. Cold does not rapidly diminish the virulence of the rabic virus. If the material is to be transmitted for a long distance, after the preparation of impressions or smears from the gray matter of the cornu Ammonis, the brain of the animal with the medulla, carefully removed to avoid contamination, may be sent in a sterilized bottle containing a mixture of equal parts of glycerin and water, which has been sterilized by boiling and cooled.

It has been found that by cauterization with fuming nitric acid of the wounds made by rabid animals, the infective agent may be destroyed even after the lapse of several hours.

ACUTE ANTERIOR POLIOMYELITIS. (Infantile Paralysis.)

Acute anterior poliomyelitis is an infectious disease occurring in epidemic and sporadic forms, affecting especially young children, and definitely, though apparently not readily, communicable.

While before 1907 epidemics of this disease were infrequent in the United States, since that time it has widely prevailed. In Europe also within the past few years the disease has been of frequent occurrence and widespread. It is characterized by an exudative inflammation of the meninges, and of the interstitial tissue of the brain, and especially the spinal cord, which may lead to destructive changes in the ganglion cells, particularly of the anterior horns, and to paralysis, atrophy, and contracture of the associated muscles.

Although a series of earlier studies had shown that the disease could be incited in monkeys by the intraperitoneal injection of an emulsion of nerve tissue from fatal cases of infantile paralysis, it was not until 1909 that Flexner and Lewis[2] succeeded in carrying the infective agent from a human case on through monkeys, by the intracranial inoculation of nerve tissue of infected animals, in a series which is now extended and apparently may be indefinitely prolonged. Then it was discovered

[1] For further details of diagnosis, see *Williams* and *Lowden*, Jour. Infect. Dis., 1906, iii, 452; *Frothingham*, Jour. Med. Research, 1905–06, N. S. ix, 471; and *Park* and *Williams*, Pathogenic Microorganisms, 6th ed., New York, 1917, p. 564.

[2] *Flexner* and *Lewis*, Jour. Exper. Med., 1910, xii, 227.

that experimental infection can be secured by inoculation into the subcutaneous tissue, blood-vessels, and nerves, and it now seems probable that under all these conditions the course of infection is through the nerves. It has been found, also, that the infective material may be present, not only in the brain, spinal cord, sensory and sympathetic ganglia, but also in the blood, spinal fluid, nasopharyngeal mucous membranes, and the lymph-nodes.[1]

The infective agent belongs among the so-called "filterable viruses" for it passes through the pores of the Berkefeld filter. Its virulence persists after drying and after long preservation in glycerin—two years or more. It is readily killed by heat—45° to 50° C. for thirty minutes, but sustains prolonged cold, though less resistant to this than to long immersion in glycerin.

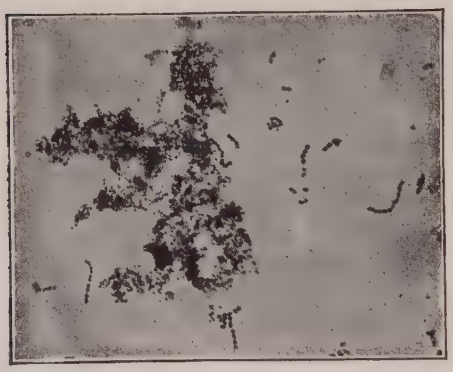


Fig. 181.—Organism Isolated from Case of Poliomyelitis.
From a preparation by Dr. Noguchi. × 1000.

Flexner and Noguchi[2] have cultivated from the brains of human cases of poliomyelitis as well as from the brains of experimentally infected monkeys, a minute organism which induces characteristic symptoms and lesions in monkeys. This spheroidal organism occurs in masses or pairs or chains, depending upon conditions of culture (Fig. 181). The individual bodies are about 0.2 micron in diameter, which is much smaller than any known cocci, and close upon the limits of visibility. By appropriate stains these organisms can be demonstrated also in the central nervous system.[3]

Cultures were at first secured from fragments of infected brain, in human ascitic fluid to which had been added a fragment of sterile tissue, such as fresh rabbit kidney, for example, oxygen being excluded by covering the liquid in the tube with a thick layer of sterile paraffin oil. The growth of the organism is manifested by a gradually increasing opalescence of the fluid. After the adaptation of the organism to the above-culture medium, it may be transferred and grown on agar and under other conditions. Cultures have been carried forward through many generations, still maintaining the capacity, under the requisite conditions, of inciting the disease in monkeys.

In addition to the organism described by Noguchi, there have been found by Rosenow[4] in the brain, cord, mesenteric lymph-nodes, tonsils, and elsewhere, irregular, short-chain streptococci or diplococci, usually

[1] For a study of the distribution of the virus from the blood, see *Flexner* and *Amoss*, Jour. Exper. Med., 1914, xix, 411.

[2] *Flexner* and *Noguchi*, Jour. Exper. Med., 1913, xviii, 461; *Flexner*, *Noguchi*, and *Amoss*, ibid., 1915, xxi, 91.

[3] *Hektoen*, *Mathers*, and *Jackson*, Jour. Infect. Dis., 1918, xxii, 89.

[4] *Rosenow*, *Wheeler*, *Towne*, *v. Hess*, and *Gray*, Jour. Infect. Dis., 1918, xxii, 281–426 (complete bibl.).

giving a green halo on blood agar media, and in some cases fermenting inulin. Under anaerobic cultivation, the organism becomes filterable and appears in every way identical with the organism described by Flexner and Noguchi. The agglutination of some of the more sensitive strains has been observed when serum of persons who have recovered from poliomyelitis has been used.

In experimentally infected monkeys the symptoms and lesions of the disease in man are fairly reproduced. The lesions in the monkey are, primarily and chiefly, cellular infiltrative changes in the perivascular lymph-spaces of the arteries and of the interstitial substance of the nerve tissues (Fig. 804). This leads to temporary occlusion of the vessels, focal hemorrhage and edema, and degeneration of the nerve tissues with necrosis and disintegration. While the brain may be involved, the lesions are especially marked in the spinal cord and medulla. (For details of the lesions in man, see page 1180.)

Communicability.—Clinical evidence of the communicability of epidemic poliomyelitis is abundant. Since it has been shown by Flexner and Lewis, not only that the nasopharyngeal mucosa in animals artificially infected by intracranial injections may contain the infective agent, but that on rubbing the virus from an infected animal over the scarified nasopharynx of monkeys characteristic paralysis may follow, one is led to assume that the discharges from the mouth and nose of victims of the disease should be properly cared for.[1] The infectious agent is present in the nasopharyngeal secretions in mild cases giving no symptoms and in contact carriers; and the occurrence of isolated cases far removed from the central epidemic focus is probably due to such carriers.

Immunity.—Flexner and Lewis have shown that a certain immunity is secured in monkeys by a successfully weathered artificial infection. But the nature of this immunity is not yet quite clear, nor are the preliminary studies on the production of immunizing sera sufficiently advanced to justify prediction of success in the immediate future.[2]

TYPHUS FEVER. (Hospital Fever; Spotted Fever; Jail Fever; Ship Fever, etc.)

The characteristic clinical lesion of the disease is the petechical skin eruption. Histologically, the chief changes are thrombosis and striking perivascular accumulations of adventitial lymphocytes and polymorphonuclear leucocytes. The vascular endothelium is swollen, and the endothelium of the sinusoids in the liver shows similar swelling and hyperplasia. The large vascular trunks often, though not constantly, show subendothelial infiltration and minute mural thrombi. Similar lesions are seen in the vessels of the central nervous system, heart, kidney, and muscles, but no other characteristic changes are found.[3]

[1] *Flexner*, Jour. Am. Med. Assn., 1910, liv, 535.

[2] For an interesting résumé of the nature, prevalence, and prevention of the disease, see *Frost*, Pub. Health Repts. U. S. Mar. Hosp. Service, 1910, xxv, 1663. See also, *Heist*, *Solis-Cohen*, and *Kolmer*, Jour. Infect. Dis., 1918, xxii, 169–188; and *Nuzum, J. W.*, ibid., 1918, xxiii, 307.

[3] *Ceelen, W.*, Lubarsch u. Ostertag, Ergebn. d. allg. Path., 1919, xix[1], 307.

It is now generally believed that the infecting agent is *Rickettsia prowazeki*, which is transmitted by means of the louse, *Pediculus humanus*.[1]

A form of typhus fever has been described in Mexico under the name Tabardillo, and in New York under the name Brill's disease.

ROCKY MOUNTAIN SPOTTED FEVER. (Tick Fever.)

This infectious febrile disease, occurring chiefly in the spring in Montana and adjacent Rocky Mountain States, is often fatal, not communicable, and without obvious characteristic lesions save petechial and other spots of the skin which mark it as one of the group of hemorrhagic septicemias.

Minute organisms, apparently belonging to the group Rickettsia, have been found within the endothelial cells of the vascular lesions.[2] The disease can be transmitted to guinea-pigs, rabbits, and monkeys, and is probably conveyed to man by the bite of infected ticks, *Dermacentor venustus*.[3]

YELLOW FEVER.

Lesions of the Disease.

Yellow fever is endemic in tropical America, occurs on the west coast of Africa, and occasionally invades the temperate zones of America.

This infectious disease of man is without characteristic lesions save for the hemorrhages and pigmentation in the skin. Such other lesions as commonly exist are those common to toxemia. The following conditions are, however, frequently present after death:

Rigor mortis is marked and occurs early. The *brain* and its meninges are usually congested and edematous. The cerebrospinal fluid is bile stained. *The skin* is of a yellow color from the presence of bile pigment, and may be mottled by ecchymoses. Ecchymoses are frequent in the mucous and serous membranes. *The heart* is of a pale or brownish yellow color and often shows ecchymoses in its substance. The myocardium is brittle, grayish yellow and may be the seat of fatty degeneration. *The lungs* may be congested and regularly contain hemorrhagic foci up to two centimeters in diameter.

The stomach often contains a characteristic dark fluid, due to altered blood pigment, similar to that which is vomited during life—black vomit. Its mucous membrane may be congested and softened, and is sometimes eroded. *The intestines* are dark-colored, often distended with gas, and often contain more or less altered blood. *The liver* in the earlier stages of the disease may be intensely congested. More frequently

[1] *da Rocha-Lima, H.*, Lubarsch u. Ostertag, Ergebn. d. allg. Path., 1919, xix[1], 159; *Strong, R. P.*, and others, Typhus Fever, with particular reference to the Serbian epidemic, Cambridge, Mass., 1920; *Wolbach, S. B., Todd, J. L.*, and *Palfrey, F. W.*, The Etiology and Pathology of Typhus, being the main report of the Typhus Research Commission of the League of Red Cross Societies to Poland, Cambridge, Mass., 1922; *Cowdry*, Arch. Path., 1926, ii, 59.

[2] *Wolbach, S. B.*, Jour. Med. Research, 1919–20, xli, 1.

[3] *Rickets*, Jour. Inf. Dis., 1907, iv, 141.

it contains but little blood and is of a light yellow color, and the hepatic cells show the changes of an intense albuminous degeneration, often much more marked than are found in any other disease except acute yellow atrophy of the liver. Areas of focal necrosis and minute subserous ecchymoses may be present. The gall-bladder is usually filled with deep yellow bile. *The spleen* shows no marked changes. *The kidneys* present an intense albuminous degeneration. The tubules usually contain masses of hyaline material and large or small hemorrhagic areas are found in the capsule and the substance.

The Excitant of the Disease.

We owe to Noguchi[1] the discovery of the organism presumably causing the disease. This is a minute protozoan, the Leptospira icteroides. It is filterable through a Berkefeld filter and is demonstrable in the blood of patients suffering from the disease. It can be cultivated on suitable media and gives the characteristic symptoms and lesions of the disease in guinea pigs and other susceptible animals.

The Mode of Infection.

It was shown by Reed and his colleagues, Carroll, Agramonte, and Lazear, that the infectious agent in yellow fever may be transmitted by the subcutaneous injection into a healthy individual of a small quantity of blood drawn from a patient in the early stage—first three days—of the disease. It has, furthermore, been shown by repeated and abundantly confirmed experiments that yellow fever may be induced in a non-immune individual by the bite of mosquitos—*Stegomyia fasciata* or *Aëdes aegypti* —which have previously—at least twelve days—bitten a patient in an early stage of the disease. Practical sanitary procedures, based upon the hypothesis that these insects act as intermediate hosts in which the (unknown) yellow-fever parasite passes one of its developmental cycles, have furnished strong evidence that it is through the intervention of these mosquitoes, and thus only, that the disease is conveyed. For it has been possible, by the prevention of access of them to yellow-fever patients through the use of netting and other precautionary measures, practically to suppress the disease in Havana, where it was formerly endemic, and to stifle epidemics elsewhere.[2] It has been further demonstrated in the most conclusive way that the infectious agent in yellow fever is not conveyed directly through the air or by fomites.[3]

[1] For a summary of the investigations which led to this discovery see *Noguchi*, J. Trop. Med., 1925, xxviii, 185.

[2] For a summary of observations relating to the mosquito as an intermediary host of the infectious organism in yellow fever, see *Reed, Carroll, Agramonte,* and *Lazear,* Philadelphia Med. Jour., 1900, vi, 790; also Jour. Am. Med. Assn., 1901, xxxvi, 431; and Am. Med., 1901, ii, 15; *Guiteras,* Am. Med., 1901, ii, 809; *Durham,* Thompson Yates' Laboratories Report, 1901, iv, 485; *Reed* and *Carroll,* Am. Med., 1902, iii, 301; also *Carroll,* Jour. Am. Med. Assn., 1903, xl, 1429. A summary and bibliography by *Goldberger* is in Bull. No. 16 of the Yellow Fever Institute, 1907, U. S. P. H. S.

[3] For a brief résumé of the reasons for the belief that the mosquito is the sole agent in the conveyance of the infectious agent in yellow fever, see *Carter,* Bull. No. 10, of the Yellow Fever Institute, 1902, U. S. P. H. S. For a discussion of mosquitos and a general review of the subject, see, also, *Howard, Dyar,* and *Knab,* The Mosquitoes of North and Central America and the West Indies, Carnegie Institution of Washington, Pub. No. 159, 1912. For the bearing of this subject upon quarantine regulations, see *Doty,* Med. Rec., 1901, lx, 649.

The application of our new knowledge of the epidemiology of yellow fever has made possible its complete eradication from tropical America.

VARIOLA. (Smallpox.)

Smallpox is an acute, readily communicable, infectious disease, especially characterized anatomically by an inflammation of the skin which passes through a series of more or less distinctive phases of papule, vesicle, pustule, with a final drying of the exudate and necrotic tissue constituting the crust.

Various phases of the exanthem are used to designate forms of the disease.

Secondary lesions are diffuse suppurative inflammation of the skin, congestion, inflammation, and ulceration of the mucous membranes, hemorrhages in the various parts of the body, swelling and ulceration of the lymphatic tissues, albuminous degeneration of the kidney, liver, and spleen, and leucocytosis.

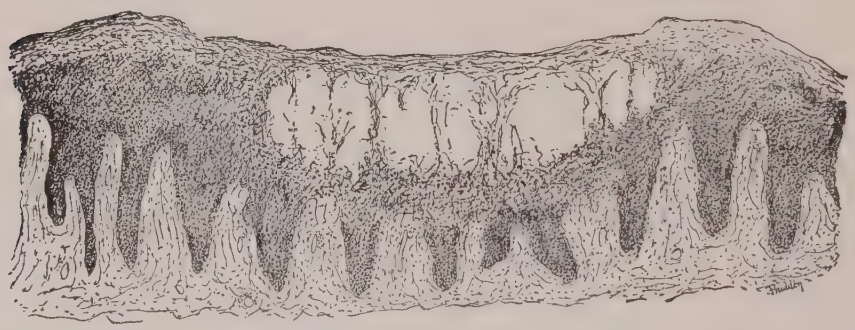


Fig. 182.—A Smallpox Vesicle of the Skin.

The skin lesion shows in general at first circumscribed areas of inflammation above the ends of the papillæ, with the development of a fluid-filled reticulum, so that vesicles more or less umbilicated are formed (Fig. 182). These at first contain a clear fluid, but by the gathering of pus cells the fluid becomes turbid and accumulates to form a pustule. Hand-in-hand with these changes the papillæ and adjacent layers of the corium may become infiltrated with cells. The contents of the pustules and the necrotic tissue above dry and form the crusts. When the changes are largely confined to the epidermis, the lesion may leave no deformity. But if the changes in the cutis are considerable, cicatricial tissue may form, leaving scars. The association of local hemorrhage with the above changes gives rise to the hemorrhagic form of exanthem.

Artificial Immunization in Smallpox.

Smallpox affords one of the most striking examples of positive and prolonged acquired immunity conferred by a successfully weathered attack of an infectious disease.

In the early days attempts were made to mitigate the virulence of smallpox acquired by exposure in the usual ways by artificial inoculation of material—virus—taken from a smallpox pustule. The usually relatively mild form of the disease induced in this way also conferred immunity. But the individual was during his immunization a source of danger to others. The great discovery of Jenner that by inoculation with virus from cowpox, immunity was secured against smallpox need not be considered in detail here. The immunity secured in this way, while not absolute, is usually effective and involves as a rule but slight indisposition. By revaccination after an interval of a few years practical protection is secured, so that the occurrence of smallpox epidemics to-day is possible only through neglect of simple and positive protective measures.

The more recent view of the immunity conferred by vaccination against smallpox is based upon the demonstration that the disease variola in man and the disease vaccinia in the bovine species are of the same nature and not different, as was formerly believed. This has been established by numerous inoculation experiments; by complement fixation tests, also, the close biological relationship between variola and vaccinia has been demonstrated.[1] The disease in the cow is a modified form of the human disease. The effect of the passage of the unknown microorganisms through the insusceptible bovine—thus runs the rationale in the new light—is so to diminish the virulence of the germ that by its subsequent inoculation in man immunity is secured without the profound disturbance which infection with a germ of unmitigated virulence would involve.[2]

The Excitant of Smallpox.

Bacteria.—The large number of studies which have been made of the skin lesions of smallpox and of vaccine lymph have shown that bacteria of various kinds are frequently present.[3] Streptococci and staphylococci are especially common in the pustules and may be present in the blood in later stages of severe or fatal cases.[4] It is probable that the pyogenic cocci are of great importance as complicating factors in the disease. But there is no evidence at hand that these or any other bacteria are its primary excitants.

Protozoa.—While it was natural that the most painstaking search should be made for bacteria in the lesions of smallpox, there have been

[1] *Kolmer*, Jour. Immunol., 1916, i, 51, 59.

[2] In *diphtheria* the perfection of the process of artificial immunization and the establishment of a precise and successful curative method are the direct results of a long, patient, logical series of animal experiments with a definite end in view, and by the use of the absolutely identified and well-known germ which induces the disease. On the other hand, it is not a little curious that in *smallpox* and in *hydrophobia* effective methods of immunization should have been perfected without precise knowledge of the microorganisms which incite the diseases, and yet by procedures which, though somewhat empirically hit upon, are nevertheless in close accord with those which the most recent studies on immunity in general have shown to be effective. Thus in both smallpox and hydrophobia the material used for protective inoculation is that which has been artificially reduced in virulence; in the one case—smallpox—by its passage through the body of a relatively insusceptible animal; in the other—hydrophobia—by drying in the air.

[3] See *Huguenin*, Lubarsch and Ostertag, Ergebn. d. allg. Path., 1897, iv, 387 (bibl.).

[4] See report by *Ewing*, Trans. Assn. Am. Phys., 1902, xvii, 213; also *Perkins* and *Pay*, Jour. Med. Research, 1903, N. S. v, 180.

from the first many obvious reasons for the conjecture that this disease as well as the other exanthemata might be incited by organisms of a different nature. In fact, as early as 1886 and 1887 bodies were found in the pustules by Van der Loeff and L. Pfeiffer, which they conjectured to be protozoa. It was not until 1892, however, when Guarnieri undertook a series of noteworthy experiments in animals, that the nature of the suspected structures in vaccine lymph became clearer. Guarnieri inoculated vaccine lymph into the cornea of rabbits and after a few days noted in the epithelial cells the appearance in increasing numbers of the structures which had been previously discovered in the contents of smallpox pustules. In some of these bodies he believed that he saw ameboid movements. These bodies, which were called "vaccine bodies," he regarded as protozoa and named the species *Cytoryctes vaccinæ*.[1]

These observations of Guarnieri on the vaccine bodies found in the lesions of both vaccinia and variola were confirmed by Wasielewski[2] and many other observers.

The vaccine bodies of Guarnieri are spheroidal, oval, or irregular structures from 1 μ to 4 or even 8 μ in diameter, staining readily with various dyes, the central portion giving in general the staining characters of nuclear substance, a peripheral zone being sometimes differentiated by cytoplasmic stains. The bodies often lie close upon the border of the nucleus of the epithelial cells, sometimes in a depression of the nuclear border. They may, however, lie in other parts of the epithelial cytoplasm. They are frequently surrounded by a clear space, which may become of considerable size. They have not been found in the nucleus.

Hand-in-hand with the increase of these bodies there are progressive degenerative processes in the epithelium of the inoculated region, with the formation of various structures characteristic of the degeneration of protoplasm under a great variety of conditions.

While many observers following Guarnieri have felt justified, largely on morphological evidence, in the belief that the vaccine bodies are protozoa, others have been led to the conclusion that many, if not all, the appearances presented can be accounted for by protoplasmic degenerations induced by other agencies. Several experimenters, indeed, by the introduction into the rabbit's cornea of chemical and other substances not at all related to the vaccine virus, have been able to induce degenerative protoplasmic structures resembling the vaccine bodies. The studies of Ewing on this subject are of especial significance.[3]

It is evident that the proof on morphological grounds alone of the protozoan nature of such minute structures is a task of extreme difficulty, associated as they frequently are with the readily stained products of protoplasmic degeneration.

In April, 1903, Councilman announced the results of a long series of studies by himself and his associates, Magrath, Brinckerhoff, and Tyzzer,

[1] This name was given because the bodies frequently lay in small spaces in the cell protoplasm, which he assumed to have been formed by the destructive action of the parasite.

[2] Consult for a most admirable summary of the subject, with original studies, photographs, and bibliography, *Wasielewski*, Ztschr. f. Hyg. u. Infectionskrankh., 1901, xxxviii, 212.

[3] See *Ewing*, Jour. Med. Research, 1904, N. S. vii, 509; 1905, N. S. viii, 233.

on the excitant of smallpox.[1] The observations of Guarnieri, Wasielewski, and others, on the vaccine body, were in the main confirmed. These observers found the vaccine bodies in the lower layers of skin epithelium before the production of the vesicles and in the advancing edges of the young vesicles. They found morphological evidence of the segmentation of the bodies and the formation of round, spore-like structures about 1 μ in diameter. Councilman further announced the discovery of other bodies, not before described, within the nucleus of the epithelial cells in the infected region in man. These intranuclear structures are circular, with a central dot, and may be seen singly or in clusters. They are from 1 to 1.5 μ in diameter. Councilman regards them as a later stage and as representing a second complex cycle of development of the smallpox parasite, and believes that they are developed from the spore-like bodies resulting from the segmentation of the intracellular vaccine body, which then penetrate the nucleus. The vaccine bodies are found both in the epithelial cells of the smallpox lesion in man and in the lesion induced by vaccination of the rabbit and calf; but the intranuclear forms have not been found in the latter animals. After inoculation of the monkey with the contents of smallpox pustules, both the intracellular and the intranuclear forms were found. It is thought probable that in smallpox the parasite undergoes complete development, passing through two cycles, an intracellular and an intranuclear, while in vaccinia only one, the primary, cycle is achieved.[2]

Calkins, from an independent study of the material furnished by Councilman, is convinced of the protozoan nature of the organisms in question and now groups them among the rhizopods.[3]

It is clear that final judgment upon the nature and significance of these minute structures must be suspended until further experiments upon suitable animals shall have furnished fuller biological data than are yet at hand, which may sustain the evidence, still largely morphological, on which these suggestive conclusions are based.[4]

The virus of vaccinia has been cultivated in vitro by the use of special methods of tissue culture.[5]

SCARLET FEVER. (Scarlatina.)

This is an infectious, readily communicable disease characterized by a diffuse skin eruption, and frequently accompanied by inflammation, either catarrhal, or croupous, or gangrenous, of the tonsils, pharynx, and larynx. Focal necroses, albuminous degeneration in the viscera, and leucocytosis with moderate eosinophilia may occur.

[1] *Councilman* and others, Jour. Med. Research, 1904, N. S. vi, 1; see also summary by *Councilman*, Am. Med., 1905, x, 689.

[2] For studies on experimental variola and vaccinia in monkeys, see *Brinckerhoff* and *Tyzzer*, Jour. Med. Research, 1906, N. S. ix, 209 *et seq.* See also, for studies on reaction of variola virus to external conditions, ibid., p. 352.

[3] *Calkins*, Protozoology, New York, 1909, p. 308.

[4] Consult for general bibl., *Freeman*, article on vaccination in Cyclopedia of the Diseases of Children, vol. v, suppl., p. 263; or *Moore*, in Twentieth Century Practice, vol. xiii.

[5] *Steinhardt, Lambert, Israeli*, and *Grund*, Jour. Infect. Dis., 1913, xiii, 294; 1914, xiv, 87; 1915, xvi, 205.

There may be acute hyperplasia or suppuration of the cervical lymph-nodes. There is very frequently an acute exudative or an acute diffuse nephritis.[1] The spleen may be enlarged. Bronchopneumonia, endocarditis, and pericarditis may complicate the disease.

The exanthem or skin eruption in scarlatina is a simple dermatitis, as the result of which the papillæ and subpapillary stratum become infiltrated with fluid or leucocytes, or both, the leucocytes being gathered especially about the blood-vessels. There may be small hemorrhages, and the acute phase of the inflammation is followed by an increased production of epithelium and an exfoliation of the superficial layers. These lesions of the skin may be, excepting the hemorrhages, very slightly marked after death.

The Excitants of Scarlatina.—Recent investigation has rendered it probable that the inciting agent in scarlet fever is a streptococcus belonging to the hemolytic group.[2] The organisms as isolated from scarlet fever patients do not all show the same cultural characteristics. While in the study of one hundred cases hemolytic streptococci were found in all, 16 per cent. of these strains fermented mannite, and 84 per cent. did not. Nevertheless it seems probable that the type of organism is a specific one and distinguishable from the forms of hemolytic streptococci causing other kinds of angina and septic conditions in general. Using the organisms isolated by them the Dicks have been able to produce scarlet fever by swabbing the tonsils with a pure culture of a hemolytic streptococcus strain. Using a Berkefeld filtrate of a culture of this organism suitably diluted as an intracutaneous injection they have been able to demonstrate that convalescent scarlet fever patients show a negative or slightly positive skin test; most of those with a history of scarlet fever show negative skin tests, while those without a history of scarlet fever give strongly positive reactions. Also the injection of serum from convalescent cases of scarlet fever render the skin tests negative. The immunization of horses with the organisms isolated from scarlet fever patients has been found to produce a serum with remarkable curative effects on scarlet fever. These facts render it very probable that the Dicks have discovered the specific type of streptococcus responsible for the disease, and the older views of Mallory[3] and others[4] of a protozoan agent will have to be abandoned.

TRACHOMA.

The inflammation of the conjunctiva, known as trachoma, has long been suspected to be of infective nature. But it was not until 1907 that

[1] For a special study of kidney lesions in scarlatina, see *Chapman*, Jour. Path., 1906, xi, 276 (bibl.).

[2] *Dick* and *Dick*, J. A. M. A., 1924, lxxxi, 301. *Dick, G. H.*, Résumé of the literature on scarlet fever, Am. J. Dis. Chil., 1924, xxviii, 484.

[3] *Mallory, F. B.*, Jour. Med. Research, 1904, N. S. v, 483; *Mallory, E. B.*, and *Medlar, E. M.*, ibid., 1916–17, N. S. xxx, 209; and *Williams* and *Lowden*, Studies from the Research Laboratory, Dept. of Health, New York, 1907, iii, 42. On the demonstration of the alleged parasites of scarlatina in blister fluids, see *Duval, C. W.*, Univ. Pennsylvania Med. Bull., 1904, xvii, 298, and Virchows Arch., 1905, clxxix, 485; and *Field, C. W.*, Jour. Exper. Med., 1905, vii, 343.

[4] For a study of intraleucocytic inclusions (Döhle bodies), see *Glomset*, Jour. Infect. Dis., 1912, xi, 468. For a study of the alleged incitement of scarlet fever in monkeys, see *Draper* and *Hanford*, Jour. Exper. Med., 1913, xvii, 517.

Halberstaedter and v. Prowazek,[1] and Greeff[2] described the occurrence in the epithelial cells of the conjunctiva during the early stages of the disease of extremely minute, round or oval bodies, smaller than the smallest cocci, and surrounded by a clear mantle which stains blue with Giemsa. The bodies do not take the Gram stain, but by the Giemsa method stain reddish or violet. They have been called *trachoma bodies*

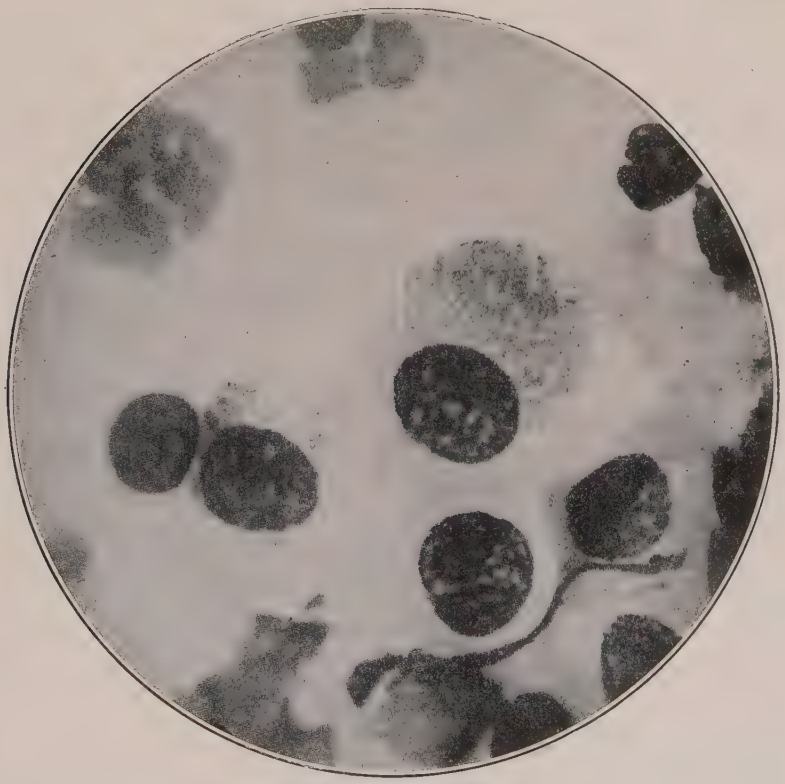


FIG. 183.—TRACHOMA BODIES.

Conjunctiva. From a preparation by Dr. Noguchi. The bodies nearly fill the cell near the center of the cut and partly surround the nucleus.

or granules, and because of the mantle have been classed by v. Prowazek as *Chlamydozoa*. They are found in the epithelial cells, often grouped in concentric masses close to the nucleus, sometimes filling and distending the cell body (Fig. 183). They vary considerably in size, increasing rapidly within their mantles, which presently they displace, but are never very abundant and may soon disappear. Their nature and significance is not clear.[3]

[1] *Halberstaedter* and *v. Prowazek*, Deutsch. med. Wchnschr., 1907, xxxiii, 1285; Handbuch d. path. Protozoen, Leipzig, 1912, i, 172 (bibl.).

[2] *Greeff*, Deutsch. med. Wchnschr., 1907, xxxiii, 914.

[3] For a study and bibl., see *Noguchi* and *Cohen*, Jour. Exper. Med., 1913, xviii, 573; and *Wolbach* and *McKee*, Jour. Med. Research, 1911, N. S. xix, 259.

In various types of inflammation of the conjunctiva, the presence of hemoglobinophilic bacilli has been demonstrated and it has been suggested that the trachoma granules found in these inflammations as well as in inflammations of the mucous membranes of other parts of the body, such as the vagina and the urethra, may be due to these bacilli.[1]

MEASLES.

This is a readily communicable infectious disease, the most prominent features of which are an intense hyperemia with inflammation of the skin, associated with catarrhal inflammation of the mucous membrane of the air passages. The inflammation of the skin is anatomically of the same general type as that in scarlatina.[2] Albuminous degeneration of the kidney or acute exudative nephritis may occur. Focal necrosis in the liver and kidneys has been described.[3]

The more common secondary lesions are bronchopneumonia, pseudomembranous inflammation of the pharynx and larynx, suppurative inflammation in various parts of the body, and diphtheria. These complications, as in scarlatina, are doubtless, in part at least, due to secondary infection with germs other than those causing the disease itself.

The excitant of measles is not known though a variety of organisms have been described.[4]

Inoculation of Measles.—Although readily conveyed in natural ways from one human being to another predisposed individual, the attempts at experimental inoculation of the infectious agent in measles in man have not led to very definite conclusions. Hektoen succeeded in two cases in inducing typical measles by the injection of material derived from the blood at an early stage of the disease.[5]

MALARIA.

The Lesions of Malaria.

The characteristic lesions of *acute* malarial infection are found in the blood, the liver, spleen, kidneys, and brain.

The alterations in the *blood* are chiefly confined to the diminution in number of the red corpuscles, due to their destruction by the parasites developing in them, and to a reduction in the hemoglobin content of those which do not contain parasites. These changes are apparently due to some toxic agent, for which there is additional evidence in the polychromatophilia and granular degeneration of the body of the red cell so often present in severe malarial infections. The evidence of some poison acting on the protoplasm of the red cells is found, not only in

[1] *Park* and *Williams*, Pathogenic Microorganisms, 6th ed., New York, 1917, p. 416.

[2] For a study of epithelial cell changes in measles, see *Ewing*, Jour. Infect. Dis., 1909, vi, 1.

[3] *Freeman*, Arch. Pediat., February, 1900, xvii, 721.

[4] For recent studies on the bacteriology of measles, see *Tunnicliff, R.*, Jour. Infect. Dis., 1918, xxii, 462; and *Hektoen, L.*, Jour. Am. Med. Assn., 1918, lxxi, 1201 (bibl.).

[5] For attempts at inoculation of measles see *Hektoen*, Jour. Infect. Dis., 1905, ii, 238. For an experimental study of measles in monkeys, see *Lucas* and *Prizer*, Jour. Med. Research, 1912, N. S., xxi, 181; and *Blake, F. G.* and *Trask, J. D.*, Jour. Exper. Med., 1921, xxxiii, 385, 413, 621.

those cells in which the organism is developing, but more abundantly in those cells in which no plasmodia are present.

The leucocytes show slight qualitative changes, there being usually present a relative increase in the large mononuclear cells. Pigmented leucocytes are often seen, and in very severe infections large macrophages loaded with pigment may be seen in the circulating blood. In severe cases the pigment, which is derived from the hemoglobin of the blood corpuscles and forms the granules in the body of the parasite, may be found free in the general circulation, but is usually soon removed by the leucocytes and the phagocytic cells of the liver, spleen, and bone marrow. The *brain* in cases of pernicious estivoautumnal fever is often much congested, and the smaller capillaries may be thrombosed, or filled with enormous numbers of the plasmodia in various phases of development; there may also be small punctate hemorrhages in the white matter. The deposition of the malarial pigment in the cortex may give to the latter a dark reddish brown color, or it may be almost black. The *spinal cord* shows similar changes.

The *liver* in acute cases may show focal necroses resembling those present in other infectious diseases. The endothelium of the liver capillaries may contain much pigment (Fig. 521, page 832), while the lumina of the capillaries may be stuffed with plasmodia in various stages of development. Thromboses of infected red blood-cells, pigment, and cell fragments are not uncommon. The *kidneys* may show albuminous degeneration, and while the intertubular capillaries may be filled with pigmented leucocytes there is not, as a rule, a great accumulation of plasmodia in the vessels. A moderate diffuse nephritis is occasionally seen. The capillaries of the mucosa of the *stomach* and the *intestines* may be filled with parasites in cases with choleraic symptoms, and there may be a considerable amount of necrosis in the epithelium of the mucosa of the intestines. The *bone-marrow* usually contains large numbers of the plasmodia, chiefly segmenting forms. A good deal of pigmentation is present, and an active phagocytosis is carried on, mainly by the giant-cell macrophages present in the marrow. Crescentic organisms may be present in the marrow even if these have not been present in the blood during life. Hyperplasia of the marrow is not seen unless the disease has continued for some time.

The *spleen* is increased in size, the pulp is softened and very dark, the Malpighian bodies are not well marked and may be necrosed. The heart muscle is fatty and capillary thrombi may be present. Microscopically, the organ is greatly congested; many of the red cells are invaded by the plasmodia which are often in the segmenting stage. There is a very active phagocytosis by the macrophages present, often so extensive as to include the red cells with their contained parasites.

In the *chronic cases* the patient may become extremely anemic with nucleated red cells in the blood and a great reduction in the number of erythroblasts. The spleen is greatly enlarged, the capsule thickened and adherent to the surrounding tissues. The cut section of the organ is of a dark brown or slaty black from the deposit of pigment. The Mal-

pighian bodies are well marked. The fibrous-tissue trabeculæ are thickened, as is the reticulum of the pulp; the pulp cells are pigmented. The liver shows a marked pigmentation, especially in the endothelium of the capillaries and in the cells of Kupffer, while occasionally there is a moderate amount of new connective tissue, which, however, does not follow, as a rule, the anatomical distribution of the connective tissue in the usual atrophic cirrhosis. In chronic poisoning the kidneys may show a chronic diffuse nephritis. The bone-marrow may remain fairly normal except for the deposition of pigment, or there may be seen a marked hyperplasia with replacement of the normal fatty marrow of the shafts of the long bones by red marrow containing normoblasts, or even megaloblasts if the disease has been long-continued and severe.

The Excitant of Malaria.

The excitant of the disease long known clinically as malaria is a small animal parasite, the *Plasmodium malariæ*, which enters the red corpuscles[1] of the blood and in the course of its development destroys them. The destruction of the cells is coincident with the maturation of the contained parasite, a phenomenon which is also coincident with the clinical appearance of the chill and its accompanying fever.[2]

These parasites of the red cell are protozoa belonging to a special sub-group, the *hæmosporidia*. For purposes of description these hemosporidia of human malaria may be classified into three species or types, each of which incites a different clinical form of disease and each of which also differs from the other types in its morphology. These types are the tertian, the quartan, and the estivoautumnal parasites.

Tertian and Quartan Types.—If the blood of a patient suffering from tertian fever be examined shortly after a chill, a number of the red cells will be found to contain small, highly refractile, actively ameboid bodies which are the early forms of the plasmodia, or merozoites. The latter often take the form of small rings surrounding a central clear space especially well seen in stained specimens (Plate I., Figs. 1–4). If the blood be examined some hours later, the small forms will have grown and small brown or black granules will be noted in the body of the plasmodium, having a very rapid motion inside the body of the parasite. If the blood be examined at the end of forty-eight hours the organism may be seen to have grown so large as to occupy nearly the whole of the red cell (Plate I., Figs. 5–12), which becomes somewhat swollen and pale, the latter effect being due to the destruction of the hemoglobin of the cell by the parasite, which thus produces the pigment granules of melanin with which it is filled. The pigment now occupies the center of the organism, which has ceased its active ameboid motion. Now small pale spots, which are the nuclei of the segmenting mature form, become easily visible

[1] While it is generally known that a few of the parasites adhere to the outer surface of the red cells the theory of *Rowley Lawson* (Jour. Exper. Med., 1914, xix, 450; 1915, xxi, 584; and 1916, xxiv, 291), that the parasites are always external to the red cells, has received little or no acceptance.

[2] For cultivation of the parasite, see *Bass, C. C.*, Jour. Am. Med. Assn., 1912, lix, 936.

(Plate I., Fig. 16), and finally the red cell bursts, and the small merozoites, each containing a nucleus, are set free to enter other red cells and to repeat the cycle. A certain portion of the free merozoites are destroyed by the phagocytic leucocytes and other cells. The free pigment left after the segmentation of the mature forms is also collected by these phagocytes. Thus after severe and prolonged attacks of malaria the leucocytes are frequently filled with pigment.

The *quartan* organism goes through a cycle similar to that of the tertian, except that the time required is seventy-two instead of forty-eight hours. There are also a few minor differences in the morphological appearance of the two organisms. Thus the small early ameboid forms of the plasmodium are much more active in their movements in the tertian than in the quartan. The pigment in the tertian is very fine; in the quartan it is often in small blocks or rods and is much coarser (Plate I., Figs. 22–25). The mass of segmenting merozoites in the tertian organism is quite irregular in shape and contains from fifteen to twenty individuals, while that of the quartan is a regular rosette in shape and the merozoites average from six to twelve (Plate I., Figs. 26–28).

Estivoautumnal Type.—The parasite of the estivoautumnal fever develops in the blood in much the same way as the other forms, with the exception that the ameboid rings are, as a rule, smaller. The signet-ring shape is more marked, and the pigment is less abundant (Plate I., Figs. 31–34). Another peculiarity of this organism is that the development of the larger ameboid forms takes place chiefly in the bone-marrow and the spleen, while in the tertian and quartan this is to be seen in the blood. Thus as soon as the plasmodium of the estivoautumnal type has grown sufficiently to occupy about one-fourth of the red cell, it disappears from the peripheral blood and can be found developing in the blood obtained by puncture of the spleen, or, in fatal cases, from the bone-marrow (Plate I., Figs. 35, 36). In such preparations the mature plasmodia may be found and the segmenting process followed (Plate I., Figs. 37–39). The organism is not so large as the tertian, as the segmenting form usually occupies only about one-half of the somewhat shrunken red corpuscle. The number of merozoites formed is about fifteen. The time of the developmental cycle in the blood is forty-eight hours.

In the blood of a patient infected with the estivoautumnal parasite, there are always found within a few days after the beginning of the disease a moderate number of crescent-shaped bodies with pigmented centers and the remnant of a red cell about them (Plate I., Figs. 43, 44). They are devoid of ameboid motion. The exact nature of these crescentic bodies was quite unknown until very recently, when it was discovered that they are cells with sexual capabilities, whose function seems to be the prolongation of the species in a cycle outside of the human body. It had long been known that certain of the large mature ameboid forms of the tertian and quartan organisms and the crescents of the estivoautumnal species did not undergo segmentation into mero-

zoites, but remained circulating in the blood. When, however, the blood containing these forms was examined in a fresh condition on a slide, and especially if the blood before being covered was allowed to remain in a moist chamber for a few minutes, changes could be seen to take place which had not been observed in perfectly fresh preparations. Certain of the mature organisms set free long, actively motile flagella which entered other mature forms. In stained preparations it could be seen that each flagellum contained some of the nuclear chromatin of the organism from which it arose, and that this flagellar chromatin united with the chromatin of the body which the flagellum entered. The crescentic forms under suitable conditions go through the same process, the male crescent giving off flagella, one of which in turn fertilizes another crescent of slightly different morphology.

Evidently this is a sexual process, and its occurrence only in blood which has been drawn from the body suggested the probability that under ordinary circumstances it takes place outside the human host. The truth of this conjecture has finally been established, and the process of fertilization and maturation of the fertilized organism has been found to occur in the stomach of a particular genus of mosquito, the Anopheles. No other type of mosquito is capable, according to our present knowledge, of acting as host to the plasmodium of human malaria, though the organism which induces malaria in birds can develop in a mosquito of the genus Culex. Whether the plasmodium can carry out its sexual cycle under other conditions than in the stomach of the Anopheles is as yet unknown. If an Anopheles bites a patient with malaria, the blood with its contained organisms is drawn into the stomach of the mosquito, the flagella are given off from the gametes and enter other mature forms and fertilize them. The fertilized organism goes through a complicated development, and the resulting sporozoite finds its way in the course of a few weeks to the salivary glands of the mosquito host, to be injected into the blood of the next person bitten. The sporozoites enter the red cells, becoming the small ameboid forms or merozoites already described.[1]

The details of the process of fertilization and the formation of the sexual cells which are capable of carrying on the cycle in the mosquito have been best observed in the estivoautumnal fevers, so that the stages will be here described in connection with the development of the crescent gametes. These crescents are formed chiefly in the bone-marrow from the small ovoid, intracellular bodies, which can early in their development be distinguished from the ordinary ameboid forms by their more abundant coarse pigment and oval outline.

The adult crescents are quite constantly present in well-developed cases, and are often found in the blood after treatment with quinine has caused the disappearance of the ameboid bodies, the power of resisting the action of drugs being much more marked in the crescents than in any other form of the plasmodium. Two types may be distinguished, both of which begin as small ameboid forms and gradually mature into

[1] For details of the process, see *Schaudinn*, Arbeiten a. d. k. Gsndhtsamte, 1902, xix, 169.

oval or crescentic organisms. One of these, the microgametocytes, or the cells producing the male elements, develops and gives off the flagellum (microgametes); the other, the macrogametes (female elements), neither form nor give off flagella. According to Marchiafava and Bignami[1] the microgametocytes are distinguished from the macrogametes by the fact that in the former (the male form) the pigment is gathered in a fairly compact mass in the middle of the crescent, the chromatin is more abundant, and the entire body stains faintly; while in the female form, the pigment surrounds the rather scanty nuclear chromatin in a ring form, the cell body stains deeply, and no flagella are given off. The crescents in the fresh blood show no ameboid motion, and even the pigment is motionless. They are either crescentic in form with the pigment collected at the center, or they may be spindle-shaped with somewhat scattered pigment, or finally short, thick ovoid bodies with pigment irregularly scattered or more frequently gathered into a ring about the nucleus. They are all contained in red blood-cells (endoglobular), the faint remnant of the red cell often being seen as a delicate line stretching between the two horns of the crescent.

The formation of flagella (microgametes) does not take place in the circulating blood; it begins only after the blood has remained on a slide for a few minutes or has remained for some time in the stomach of the mosquito. These flagella, usually about four in number, bud out from the periphery of one of the microgametocytes, which has assumed a spherical instead of a crescent shape, and grow to a length of three to five times the diameter of the red cell. They are either pointed or bulbous at their extremities, or they present swellings at irregular intervals. Their motion in warm-stage preparation is rather rapid, and they finally become detached and move about free in the serum (Plate I., Figs. 45, 46, 47). The pigment during this process usually remains at the center of the spherical microgametocyte and is actively motile, but in preparations stained to show the nuclear chromatin the latter may be seen to penetrate the flagella in the form of long thin rods which remain after the flagella become detached. The shell of the red cell in which the crescent has developed can rarely be seen in fresh preparations of the flagellate forms. These flagella penetrate the body of one of the macrogametes present on the slide and fertilize it.

This process, which we have followed in an artificial preparation, seems necessary for the continuance of the race, and is normally carried out in the gastric tract of the mosquito of the genus Anophelos. The actual entry of the microgamete (spermatozoon) into the macrogamete has been observed by MacCallum[2] and others in fresh-blood preparations.

If a patient in whose blood mature crescents are present is bitten by the mosquito, the parasites develop in the stomach of the insect, and at the end of two days the fertilized forms may be found adherent to the wall of the stomach as small pigmented oval bodies quite similar to the early forms of the crescents developing in the human bone-marrow.

[1] Other observers assert that in the male forms the pigment is scattered throughout the plasmodium.
[2] *MacCallum, W. G.*, Jour. Exper. Med., 1898, iii. 117.

Description of Plate I.

Hæmatozoa of Tertian Malaria.

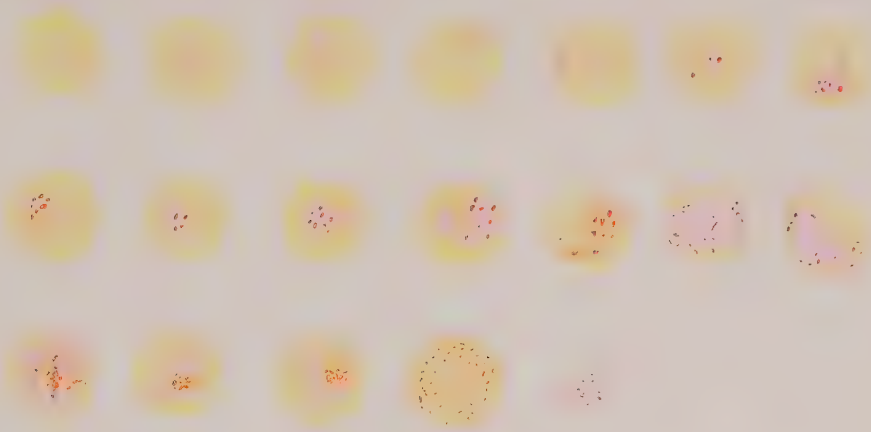
Figs. 1 to 4 ....Small ring-shaped merozoites of tertian malaria; 2 and 3, multiple invasion of a single red cell.
" 5 to 12....Ameboid forms of gradually increasing size.
Fig. 13 .....Large ameboid form in which the pigment is beginning to collect as a preliminary to segmentation.
" 14 .....Pigment still more clumped, and the pale areas representing nuclei begin to be marked.
" 15 .....Segmenting form with an irregular mass of merozoites.
" 16 .....More symmetrical type of segmentation with central block of pigment.
" 17 .....Free merozoites after leaving the red cell.
" 18 .....Gamete.
" 19 .....Microgametocyte with flagella or microgametes.

Hæmatozoa of Quartan Malaria.

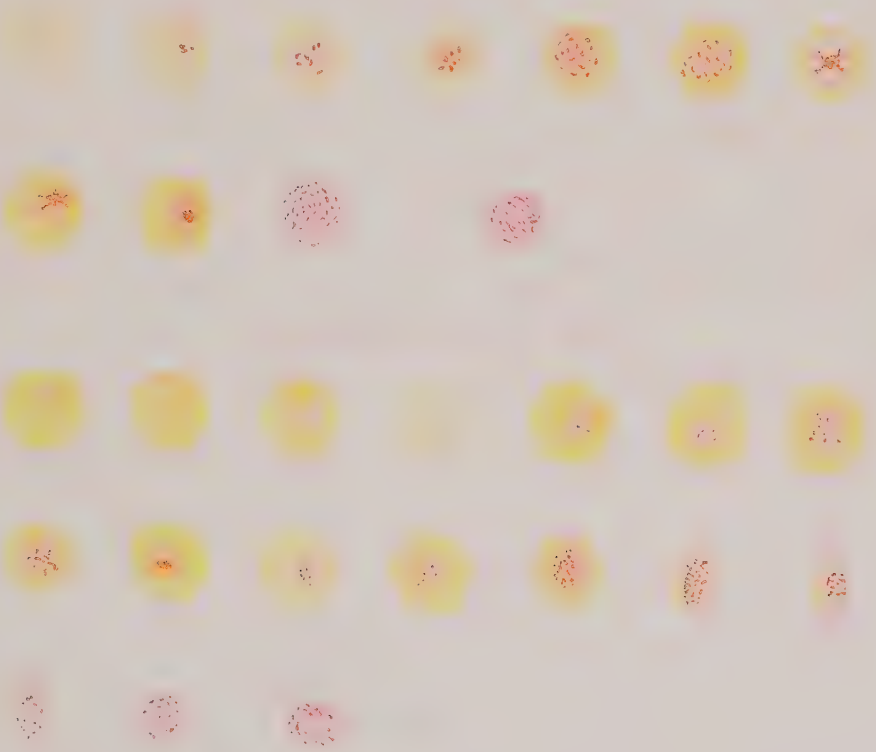
Figs. 20 and 21..Small ring form of merozoites.
" 22 to 25....Ameboid forms with coarse pigment.
" 26 to 28 ...Segmenting forms.
" 29 .....Gamete.
" 30 .....Microgametocyte with microgametes in the process of formation.

Hæmatozoa of Estivoautumnal Malaria.

Figs. 31 to 34 ...Small ring forms, some of them on the surface of the corpuscle; 32 and 33, multiple invasion of the red cell.
" 35 and 36...Ameboid forms found in the peripheral circulation.
" 37 to 39....Large ameboid forms and segmenting parasites found only very rarely in the peripheral circulation, but abundantly in the spleen and bone-marrow.
" 40 to 42 ...Young crescentic forms not found in the peripheral circulation, but chiefly in the bone-marrow.
" 43 and 44..Adult crescents or gametes, found abundantly in the peripheral blood.
" 45 and 46..Microgametocytes becoming oval and preparing to give off microgametes.
Fig. 47 .....Microgametocyte giving off microgametes.



Hematozoa of Tertian Malaria



Hematozoa of Aestivo-Autumnal Malaria

Two days later the parasites or oöcysts are much larger and have a distinct capsule, while by the sixth day they may measure from 60 to 80 μ in diameter. They contain numerous small particles which are nuclei due to the frequent division of the original nuclear material, and the capsule is much thicker. At the end of a week the parasite contains a large number of slender thread-like rods with pointed extremities, each one of these rods having nuclear chromatin. The parasite or oöcyst projects through the wall of the stomach into the cœlomic cavity of the mosquito host, and when it ruptures these minute rods or sporozoites are carried by the lymph currents to the salivary glands, from which they may be injected with the saliva when the female Anopheles bites another subject.

The sporozoites, after entering the circulation of man, attack the red cells, and become the small ameboid forms described above. In two or three weeks the formation of the gametes takes place, and the crescent forms appear in the blood.

That the infection of man in this way is possible has been abundantly proved by allowing mosquitos infected with estivoautumnal organisms to bite healthy persons, who, after a period of incubation of about ten days, are seized with an estivoautumnal type of fever, and the characteristic organisms, though not present previously, are then to be found in the blood. The mature forms of gametes of the tertian and quartan fevers undergo a course of development very similar to that of the parasites of estivoautumnal fever, and are derived from the blood of the infected patient by the female of the same genus of mosquito, the Anopheles (Plate I., Figs. 19 and 30). The sporozoites find their way to the salivary glands of the mosquito and while the Anopheles is biting enter the blood of the person infected. These sporozoites then enter the red cells as the small ameboid forms and carry on the sexual cycle in the blood until either the tissues of the body finally overcome the parasite, or treatment with quinine destroys the merozoites by means of the toxic action of the drug on these immature forms.[1]

WHOOPING-COUGH. (Pertussis.)

Whooping-cough is a readily communicable, infectious disease usually associated with catarrhal inflammation of the upper respiratory passages. It may be complicated by bronchitis or pneumonia. Hyperplasia of the lymph-nodes of the laryngeal and bronchial districts may occur. Increase in the lymphocytes of the blood is frequent in the early stages. Immunity is usually secured by an attack.

[1] A general bibliography of malaria to 1895 is contained in the excellent monograph of *Thayer* and *Hewetson*, The Malarial Fevers of Baltimore, Johns Hopkins Hosp. Rep., 1895, v, 1. See, also, *Marchiafava* and *Bignami*, on Malaria, in Twentieth Century Practice, New York, 1900; *Lühe*, Centralbl. f. Bakteriol., 1900, xxvii, 367, 436; 1900, xxviii, 384; and *Eysell, A.*, Mense, Handbuch d. Tropenkrankheiten, 2d ed., Leipzig, 1913, i, 97 (bibl.). For a study of structure and biology of Anopheles, see *Nuttall* and *Shipley*, Jour. Hyg., 1901, i, 4. For practical directions for the identification and study of mosquitoes, see *Alcock*, Entomology for Medical Officers, London, 1911; and *Howard, Dyar*, and *Knab*, the Mosquitoes of North and Central America and the West Indies, Carnegie Institution of Washington, Pub. No. 159, 1912.

The organism described by Bordet and Gengou[1] seems most probably to be the specific agent. This organism is a small, ovoid, short bacillus showing irregular staining. It stains with some difficulty, requiring the use of dilute carbol-fuchsin or other strong stains to color it satisfactorily.

Mallory[2] has shown that the bacilli can be demonstrated in large numbers lying among the cilia of the tracheal and bronchial mucosa. The disease can be transmitted to young dogs and monkeys, with the production of the same lesions; and a complement fixation can be demonstrated between the organs and the blood of infected animals and of children suffering from whooping-cough.

The poles often stain more deeply than the centers. The bacillus is negative to Gram. The organism is grown only with difficulty and upon a special medium of glycerinated extract of potato to which has been added an equal volume of sterile defibrinated rabbit or human blood. The organism is strictly aerobic and in ascitic broth may remain alive for some months.[3] Bordet and Gengou report that a specific complement fixation can be obtained in the serum of patients suffering from the disease. Protective vaccination has been practised with fair results; whether the course of the disease can be influenced is still doubtful.[4]

ACUTE RHEUMATISM.

While the excitant of acute articular rheumatism is as yet unknown,[5] there is no reason to doubt that it belongs to the infectious agents—probably streptococcus viridans. Organisms in great variety have been isolated from the joint fluid in acute rheumatism, usually a streptococcus. In the blood, streptococcus and staphylococcus also have been isolated, but in many instances the blood is sterile. Inasmuch as the probable port of entry of these organisms is the tonsil, attempts have been made to connect by serological measures organisms cultivated from the throat with the disease, but this has not proved satisfactory. In one instance for example thirteen strains of hemolytic streptococci cultivated from the throats of persons suffering from acute rheumatism when tested showed no evidence of being serologically related.[6] Nor has the attempt succeeded in linking streptococcus viridans, which is so often found in the heart valves in endocarditis, with rheumatism. The only characteristic lesions are the nodules described by Aschoff (Fig. 183*a*), which occur in the tissues about the joints, in the vessels and the myo- and endocardium.[7] The synovial membranes of the inflamed joints are thickened and injected; occasionally some hemorrhages are present. The exudate is pale yellow, cloudy, occasionally contains pus and syncytical cells and fibrin. The tissues about the joints are swollen and edematous. Occasionally small

[1] *Bordet* and *Gengou*, Ann. de l'Inst. Pasteur, 1906, xx, 731.

[2] *Mallory* and *Hornor*, Jour. Med. Research, 1912–13, N. S. xxii, 115; *Mallory*, *Hornor*, and *Henderson*, ibid., p. 391.

[3] *Wollstein*, Jour. Exper. Med., 1909, xi, 41.

[4] For value of vaccines in pertussis, see *Barenberg*, *I. H.*, Am. Jour. Dis. Child., 1918, xvi, 23.

[5] *Mac Callum*, *W. G.*, Jour. Am. Med. Assn., 1925, lxxxiv, 1545.

[6] *Andrewes*, *Derick* and *Swift*, Jour. Exper. Med., 1926, xliii, 13 (bibl.).

[7] *Whitman* and *Eastlake*, Arch. Int. Med., 1920, xxvi, 601.

ulcerated patches are found on the cartilaginous surfaces. The frequency with which endocarditis occurs has been mentioned. Pleuritis and pericarditis are also frequent, pneumonic and meningitic complications less so. Erythema nodosum is a common accompaniment. Erythema multiforme may also occur. Subcutaneous nodules are not uncommon.[1] It is sometimes difficult to differentiate rheumatic fever with petechiæ from the purpuras, as the hemorrhages into the joints

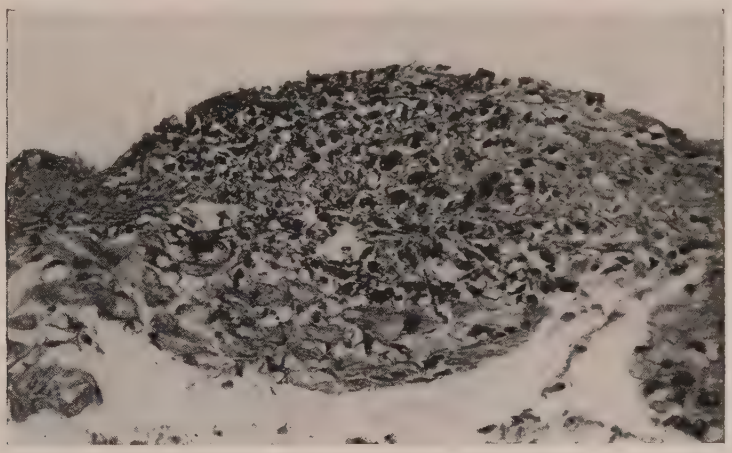


FIG. 183*a*.—ASCHOFF BODY IN ENDOCARDIUM IN CASE OF ACUTE RHEUMATISM. × 200.

give the same symptoms. The course of the two diseases is however entirely different.

TRENCH FEVER.[2]

A febrile, rarely fatal disease, described under this name, was very prevalent among the troops during the world war, at some periods amounting to one-third of all cases of illness, and occurring chiefly among those who had been in the trenches. The incubation period varies from six to twenty-two days. In many ways, the disease resembles an abortive type of typhoid fever. The temperature curve is a peculiar one, rising rapidly to 103° or 104°, often falling to normal by the third day, and rising again roughly at five-day intervals. The pulse rate is usually slow in relation to the temperature. The symptoms include headache, constipation, and pain which is especially frequent over the shins and calves of the legs and seems to occur at the point of insertion of the muscles. There are no joint involvements. The spleen is not enlarged. The urine shows no characteristic change.

The infectious nature of the disease has been demonstrated,[3] both the red corpuscles and the blood serum being infective. The virus can be

[1] *Fahr*, Virchows Arch., 1921, ccxxxii, 134.

[2] *Swift, H.*, Arch. Int. Med., 1920, xxvi, 76.

[3] *McNee, Renshaw*, and *Brunt*, Brit. Med. Jour., 1916, i, 225; and *Byam and others*, Jour. Am. Med. Assn., 1918, lxxi, 21, 110, 188. See, also, Trench Fever, Report of Commission, Medical Research Committee, American Red Cross, Oxford, 1918; and *Bruce, J.*, Jour. Hygiene, 1921, xx, 258.

passed through a Berkefeld filter. The disease can undoubtedly be transmitted by the body louse; but that this is the only means of conveyance has not yet been proved. While some observers have thought that it is a type of relapsing fever due to the Spirochæta obermeieri, others have believed that the disease is a special form of spirochetosis, the organism of which has not been demonstrated. A variety of bacteria and other parasites have been isolated, but none has been proved to be the specific etiological factor.

INFECTIVE JAUNDICE.

Epidemics of jaundice have been recognized since the Greek period of medicine, chiefly among the armies in the field. In recent years this type of jaundice has been known as Weil's disease. The clinical symptoms are vomiting and diarrhea, accompanied by high temperature. There may be blood in the stools. Shortly after the onset of the first symptoms jaundice appears; and there is usually a leucocytosis, and bile, albumin, and casts in the urine. The liver is frequently enlarged, the spleen rarely to a palpable size. Hemorrhages into the skin, hematemesis, and hemoptysis are not infrequent. On post-mortem examination, the mucous membranes of the stomach and intestines may be found to be swollen, with submucous and subperitoneal hemorrhages. The liver shows fatty changes and some infiltration with leucocytes; there is a good deal of biliary stasis in the finer bile capillaries; and occasionally an extreme lesion resembling acute yellow atrophy is seen. The kidneys show hemorrhages into the tubules, inflammatory exudate in the interstitial tissue, and swelling and degeneration of the tubular epithelium.[1]

A spirochete can usually be demonstrated in the urine, especially when after centrifugalization of the specimen the sediment is mixed with india ink and a smear is made. The organism is the *Spirochæta icterohæmorrhagiæ* (page 143). This is frequently found in rats, which presumably are the means of carrying the infection.[2]

TULAREMIA.

In 1911 McCoy,[3] who was investigating the possible conditions of transmission of plague in animals, found that some of the rodents in the western portions of the United States suffered from a disease which resembled the plague. He isolated the agent, *Bacterium tularense*. Recently it has been discovered that this organism is the cause of a serious infection in man. After inoculation by the insect vector, the disease sets in within forty-eight hours with high fever, a local sloughing inflammatory lesion with pain and usually swelling in the regional lymphnodes. These nodes become inflamed and frequently suppurate. The

[1] *Lubarsch, O.*, Lubarsch u. Ostertag, Ergebn d. allg. Path., 1919, xix[1], 560; *Inada, K.*, Jour. Exper. Med., 1917, xxvi, 355.

[2] *Dawson, B., Hume, H. E.* and *Bedson, S. P.*, Brit. Med. Jour., 1917, ii, 345. For serum treatment see *Inada, R., and others*, Jour. Exper. Med., 1918, xxvii, 283; and *Kaneko* and *Okuda*, ibid., 305.

[3] *McCoy, G. W.*, and *Chapin, C. W.*, J. Infect. Dis., 1912, x, 61; and *Francis, Edward*, J. A. M. A., 1925, lxxxiv, 1243 (complete bibl.).

fever is of a septic type, lasting from three to six weeks, and convalescence is slow. The disease may develop into a general sepsis and is then not infrequently fatal. Jaundice may be present.

Under ordinary conditions it affects chiefly the rural population, particularly those who work in the fields. The vector in this case is probably the deer fly *Chrysops discalis*. A number of the human cases have been infected through some slight trauma or through an abrasion in the skin of the hands.

The organism is a small non-motile gram-negative bacillus, which grows well on some of the special media and readily infects guinea-pigs, a fact useful in diagnosis of obscure clinical cases. The high specific agglutinin which is found in the blood is of great diagnostic value in those with no culturable local lesions.

So rare and local a disease excited but little interest until it was found that laboratory workers and persons skinning and dressing rabbits, might, because of the ready susceptibility of man, develop the disease. It was also found to be capable of causing an acute conjunctivitis.

The lesions are those of acute suppurative adenitis, with leukocytosis and occasionally a bacteremia. The changes in the other organs, so far as they have been observed are those of an acute infectious process. The spleen is soft, congested and pulpy. It is filled with yellowish necrotic foci. The liver may or may not contain similar foci. The kidneys are intensely congested. The lungs in one fatal case contained many necrotic areas, the largest about 2 cm. in diameter. These areas were surrounded by a lymphocytic infiltration and occasionally a fibrous capsule.

GRANULOMA INGUINALE.

This disease is frequent throughout the tropics and found also in the United States, particularly in the southern part. It is a chronic, infectious, ulcerative, granulomatous condition of the skin and subcutaneous tissues usually limited to the genito-anal and genito-crural regions, though lesions of the mouth and face, the back and the leg have been reported. There is nothing characteristic about the gross aspect of the lesions. Since in the male it usually begins on the penis, in the female on the labia minora, and because of the limitation to the genital region it has been looked upon as transmitted by sexual contact, but this is not proved. The malady is met with in both sexes, is chronic, and shows little tendency to heal spontaneously. It is largely, if not wholly, limited to the negroid races. Since the report of Donovan in 1905 of the presence of rod-like bodies within the mononuclear cells in the lesions of granuloma inguinale, there has been considerable controversy over the nature of the excitant. Largely this has centered about the identification of the included bodies with the Friedländer group of bacilli, with which they seem morphologically identical. The extreme views may be expressed by the view of Walker[1] who pronounces them identical, and the opinion of McIntosh[2] who states that they are unrelated. The latter

[1] *Walker, E. L.*, J. Med. Res., 1918, xxxvii, 427.
[2] *McIntosh, J. A.*, Jour. Am. Med. Assn., 1926, lxxxvii, 996 (bibl.).

accepts the designation Calymmatobacterium granulomatis as the preferable term. The distinctive feature of this granulomatous lesion is the presence of the intracellular, Gram negative, encapsulated, rod-like Donovan bodies found in the mononuclear cells, best demonstrated by punctures of the deeper portions of the lesion so as to be free from the polymorphonuclear reaction of the surface. Culturally the largest number of investigators have secured bacteria similar to the Friedländer group but the etiological importance of these cultivable organisms is debatable. Various spirochetes have been reported as causative agents. Successful transmission from one individual to another by injection of material from an existing human lesion has been accomplished. One notable peculiarity of the disease is its prompt improvement following intravenous injections of tartar emetic.

VERRUGA PERUVIANA.

Verruga peruviana is a disease endemic in Peru on the western slopes of the Andes and characterized by an eruption on the skin and occasionally on the mucous membranes of the nose and mouth. According to the size and stage of the eruption the lesions may be termed miliar, nodular, or mular. The opinion is often expressed that the eruption may appear in the internal organs, but this has not been substantiated.[1] Competent investigators are convinced that the so-called verrugous lesions of the internal organs have been mistaken diagnoses of other diseases, notably of tuberculosis. The mortality ascribed to this disease is exaggerated for verruga is rarely fatal, and the long continued fevers attributed to it may be due to malaria or Oroya fever.

In contradistinction to the belief held by the Peruvian physicians and others that verruga and Oroya fever are stages of the same disease, the Harvard group of investigators hold that they are two distinct diseases. The organism, Bartonella bacilliformis, is not found in verruga, either in the blood or the nodules; the severe anemia of Oroya is not present in uncomplicated cases of verruga; repetition of Carrion's experiment of inoculation through the scarified skin with material from the nodules of cases of verruga caused only local lesions which healed and gave none of the symptoms of Oroya fever. Furthermore they were able to reproduce verrugous lesions in animals and carry them through several animals in series without the findings or symptoms of Oroya fever.

Verruga peruviana constitutes a special form of granuloma characterized in its early stages by the formation of new blood vessels in œdematous connective tissue. The prevailing type of cell is the angioblast, forming masses or islands of closely placed cells, and there is an invasion of the connective tissue by lymphocytes, plasma cells and leucocytes. As the lesion progresses we have the formation of fibroblasts and the deposit of collagen fibrils. Different stages may resemble fibrosarcoma, myxosarcoma, or angioma somewhat.

[1] *Strong, Tyzzer, Brues, Sellards* and *Gastiaburu*, Harvard School of Tropical Medicine Report of First Expedition to South America, Harvard Univ. Press, Cambridge, 1915; see also preliminary report Jour. Am. Med. Assn., 1913, lxi, 1713.

No microorganisms are found in the unbroken nodules.

The opinion prevails in Peru that one attack of verruga protects against subsequent attacks. Strong and his coworkers found animals resistant for at least six months after inoculation with material from verruga nodule and they believe that the disease is due to a virus, though cultivation and filtration experiments were negative.

The disease is not markedly contagious. In hospitals there is no tendency to spread. It seems very probable that it is transmitted by some arthropod, whether a species of tick, mosquito or Phlebotomus is a question. Townsend[1] incriminates Phlebotomus verrucarum.

The cutaneous lesions known as verruga miliar, v. nodular and v. mular have been reproduced in monkeys by inoculation with Bartonella bacilliformis[2] the organism causing Oroya fever. The demonstration of Bartonella bacilliformis within the endothelial cells, remarks Noguchi, distinguishes the lesion from others simulating it.

Noguchi has isolated from a patient with human verruga an organism which he considers culturally, morphologically and pathogenically identical with the Bartonella bacilliformis of Oroya fever. Complete immunity for the one is established by the other, indicating their identity.

OROYA FEVER.

Oroya fever has been a known and important endemic and epidemic disease of Peru since ancient times. It is accredited with the destruction of one-fourth of the invading army of Pizarro in the 16th century; in 1870 there were 7000 deaths reported due to this malady among the employees of the Central Railway operating between Lima and Oroya, and it was at this time that the name Oroya fever was given to the ailment, though the disease did not appear to be contracted in the city of Oroya itself. Again in 1906 there were 200 deaths among the employees of the Central Railway due to Oroya fever. In 1885 Daniel Carrion, a medical student, vaccinated himself with material from a verruga nodule in an attempt to show the relation of verruga peruviana to Oroya fever. The experiment resulted in the death of the experimenter and the appellation "Carrion's disease" to the malady.

Among the various organisms looked upon as cause of the disease may be mentioned acid-fast bacilli, colon-like and paratyphoid bacilli, and protozoa. In 1909 Barton described certain "X" bodies within the red blood corpuscles that are now looked upon as the specific cause. Strong, Tyzzer, Sellards, Brues, and Gastiaburu[3] look upon these organisms as the specific cause and proposed the name Bartonella bacilliformis. The bodies are small globular, curved, or rod-shaped, motile organisms occurring within the red cells and vary in size from 0.5 to 1 μ in diameter in the globes to 1.5 to 2.5 μ in length in the rod-shape and may be observed in fresh or in stained preparations. Strong and his coworkers were

[1] *Townsend*, Jour. Am. Med. Assn., 1913, lxi, 1717.

[2] *Noguchi*, Jour. Exp. Med., 1927, xlv, 455; ibid., 1927, xlv, 175; ibid., 1927, xlv, 781.

[3] *Strong*, *Tyzzer*, *Sellards*, *Brues*, and *Gastiaburu*, Report First Expedition to South America, 1913, Harvard School of Tropical Medicine, Cambridge, 1915.

unable to grow the organisms in vitro or to reproduce the disease in animals.

The Harvard commission found that the Peruvian viewpoint was that verruga peruviana in the severe form began as the fiebre grave of Carrion and terminated in the eruptive stage with the verruga nodules which are termed "miliar," "nodular," or "mular" according to their various characteristics. Verruga nodules were found free from Bartonella bacilliformis, typical febrile cases were found with Bartonella bacilliformis in the blood and without the verruga nodules, and finally verruga could be reproduced in animals by inoculation with material from the nodules while injections of blood containing Bartonella bacilliformis failed to cause either type of disease. It was decided that the diseases were two distinct entities, either of which might be superimposed upon the other. Likewise coincident typhoid and paratyphoid fever with verruga, and also coincident malaria has done much to confuse the two diseases, and of interest is the commission's finding of tuberculous nodules reported as "internal eruption" or Oroya Fever.

Oroya fever may be looked upon as a febrile disease which may terminate in death within 3 to 4 weeks in severe cases, characterized by the presence of Bartonella bacilliformis within the red cells of the peripheral blood and in the endothelial cells, a rapid and very pernicious anemia, and severe prostration. Death results in 30 to 40 per cent of the severe cases but in some epidemics is as high as 75 per cent. Histologically the most marked changes are found in the liver, spleen, bone marrow, and lymph nodes. Toxic degeneration of the liver, splenic infarcts, marked phagocytosis of red cells in bone marrow, and in the lymph nodes swollen endothelial cells filled with Bartonella bacilliformis. The blood may resemble that of myelogenous leukemia.

Noguchi and Battistini[1] were able to cultivate on leptospira media the organism Bartonella bacilliformis from the citrated blood of a fatal case of Oroya fever. The blood was kept at refrigerator temperature for 28 days in transit from Lima and growth took place in the above media after 4 days in the incubator at 37° C. and an additional incubation of 4 days at room temperature. The initial growth is extremely delicate, invisible to the naked eye. In subcultures they were able to obtain growth on agar to which human or rabbit blood had been added. The organism withstands a pH range of 6.8 to 8.4, optimum 7.8, is an obligate aerobe, motile under certain conditions, ferments none of the ordinary carbohydrates, pleomorphic, and stains negatively with Gram stain. In leptospira semi-solid media many coccobacillary forms occur and also a huge, abnormal, spirochetal type.

Noguchi[2] reproduced both Oroya fever and verruga-like disease in Macacus rhesus monkeys by inoculation of Bartonella bacilliformis, and from these animals recovered the organism from the peripheral blood and from the verruga nodules. By allowing long periods of feeding on both infected animals and normal he succeeded in transmitting the febrile

[1] *Noguchi* and *Battistini*, Jour. Exp. Med., 1926, xliii, 851.
[2] *Noguchi*, Jour. Exp. Med., 1926, xliv, 533, 697, 715, 729; ibid., 1927, xlv, 437, 455.

disease in a mild form through the tick Dermacentor andersoni. That a real infection was obtained was shown by blood culture.

In the experimental infections of M. rhesus Noguchi recognizes three types: 1, severe fatal with extreme anemia; 2, relatively benign accompanied by localized lesions in the skin similar to human verruga; 3, mild systemic disease involving lymphatic nodes and blood. In one case he found small, verruga-like nodules in the lungs and spleen.

Summed up the results of Noguchi's experiments are represented by the following:

Bartonella bacilliformis introduced locally produces verruga-like nodules which may persist for months, but remain local despite the fact that the surrounding skin may be bathed with blood resulting from injury. Regression in 4 to 5 months is the rule.

When the verrugous mass ruptures at the beginning of regression a slough, with quick healing and scar formation results. If injured or surgically operated upon during the developing stage a renewed vigor and spread beyond the previous limits in the form of "verruga mular" may obtain; in other words "it becomes malignant."

Verruga-like nodules are not always the result of the application of infectious material to the scarified skin; intradermal inoculation almost invariably gives rise to a nodule.

Localization of Bartonella bacilliformis in the skin of experimental animals is not determined by mechanical factors since scarification or intradermal injections of foreign substances into the infected monkeys do not give rise to verruga formation.

The evolution of the skin nodules may be divided into four stages; incubation period, initial stage, mature and vascular stage, and regression. In the initial stage the lesion is a "pure angioendothelioma," but later is complicated by connective tissue proliferation, and occasionally by penetration of epidermis into the lesion. The demonstration of Bartonella bacilliformis within the endothelial cells distinguishes the lesion from others simulating it.

The cutaneous lesions known as verruga miliar, nodular, and mular have been reproduced in monkeys. Likewise by intravenous inoculation with Bartonella bacilliformis there has been reproduced in monkeys a disease comparable to Oroya fever in man with the focal necroses in the liver, splenic and lymph node hyperplasia, the bone marrow changes and severe anemia, and the characteristic invasion of the red blood cells by the organism.

Culture on leptospira media for a period of four to five weeks at 25° C. is recommended as best method of demonstrating the Bartonella bacilliformis. The organism may live as long as 120 days on such media, and may be preserved in citrated blood or nodules for similar periods.

INFECTIOUS DISEASES OF UNKNOWN ORIGIN.

PROTOZOA.—Notwithstanding the great increase in our knowledge of infection within the past few years, there are still several diseases obviously of this class whose inciting factors are unknown to us. We are now beginning to realize that we must

not confine our search in this class of diseases to the bacteria alone; but that among the protozoa may be found most important infective agents. In this latter group of organisms the culture methods applicable to the bacteria do not furnish the necessary data for the establishment of etiological relationships. While the pathogenic significance of the malarial protozoon was determined without cultures, and the pathogenic significance of other protozoa has become probable on morphological grounds, the desirability of artificial culture methods in the study of protozoa is daily becoming clearer. But it is well to remember that many protozoa pass through complex life cycles so that simple cultures cannot be expected to yield as illuminating results as do cultures of the more simply organized bacteria and yeasts.

Ultramicroscopic Microorganisms.—In the search for the inciting agents of infectious diseases which have as yet baffled investigation, it should be borne in mind that it is quite possible that bacterial and other microorganisms may exist which are ultramicroscopic; that is, so small as to be invisible with such microscopic resources as we at present possess. In one instance, the infectious pleuropneumonia of cattle, Nocard and Roux by a special technique[1] have been able to isolate an organism so small that its morphological characters could not be learned even with the highest available magnification. Experiments with the filtration of infectious material, especially from certain communicable diseases of animals, through porcelain filters whose pores are so fine as to retain ordinary bacteria, have shown that the infective agent may pass these filters and, though revealing no morphological elements, still be virulent. Among the more important of the ultramicroscopic infective agents which have been found to pass the pores of porcelain filters are those inciting contagious pleuropneumonia of cattle, anterior poliomyelitis, yellow fever, foot-and-mouth disease, and rinderpest of cattle. The possibility of the existence of ultramicroscopic organisms must then be held in mind in our summaries of infectious diseases whose inciting factors, though persistently sought, are still unknown.[2]

THE INFECTIOUS DISEASES OF ANIMALS.

The study of comparative pathology is of great and increasing importance, and already much light has been thrown on the nature of human diseases by the study of the diseases of the lower animals.

The scope of this book does not permit of more than an occasional reference to animal diseases, but the reader may consult: *Moore*, The Pathology of the Infectious Diseases of Animals, 1906; *Nocard* and *Leclainche*, Les Maladies Microbiennes des Animaux, Paris, 1898; *Frieberger* and *Frohner*, Lehrbuch der speciellen Pathologie und Therapie der Hausthiere, 1896; also *Kitt*, Text-book of Comparative General Pathology, Eng. Trans. by *Smith* and *Cadbury*, 1906.

BIBLIOGRAPHY OF THE INFECTIOUS DISEASES.

For a fuller treatment of the themes considered in this chapter the reader may consult among the larger works:

Kolle and *Wassermann*, Handbuch der pathogenen Mikroorganismen, 2d ed., 1908–13.

Kolle and *Hetsch*, Experimentelle Bakteriologie u. d. Infectionskrankheiten, 1919.

Among the smaller works may be mentioned:

Hiss and *Zinsser*, Text-book of Bacteriology, 5th ed., New York, 1922. This admirable work presents a concise but comprehensive epitome of modern bacteriology, especially in those aspects which are of practical value to students and practitioners of medicine.

Park and *Williams*, Pathogenic Microorganisms, 8th ed., Philadelphia, 1925. Presents important hygienic and public-health aspects of the subject.

[1] For a description of collodion sacs used in the study of ultramicroscopic organisms and agglutination, and for other purposes see *McCrae, J.*, Jour. Exper. Med., 1900, v. 635; and *Rosenau*, Laboratory Technique, Bull. 7, Hyg. Lab., U. S. P. H. S., Washington, 1902. For details of method of making sacs of standard permeability, see *Farmer, C. J.*, Jour. Biol. Chem., 1917, xxxii, 447.

[2] For a summary of investigations on infectious diseases of unknown origin, see *Hektoen*, Jour. Am. Med. Assn., 1903, xli, 405, 493; *Roux*, Bull. d. l'Inst. Pasteur, 1903, i, 7, 49 (bibl.); *Wolbach, S. B.*, Jour. Med. Research, 1912, N. S. xxii, 1; *Lipschütz, B.*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 1913, viii, 345 (bibl.), *Simon*, Physiol. Rev., 1923, iii, 483.

CHAPTER X.

MALFORMATIONS.

General Considerations.

THE classification of malformations is difficult, both because of the complexities of development not yet wholly understood, and because of our ignorance of many subtle phases of nutrition and inheritance in general. We shall here attempt little more than a catalogue of some of the more striking or common developmental defects, with a suggestion of grouping for convenience rather than for scientific accuracy.[1]

The individual may be subject to abnormal conditions during embryonic life which lead to changes analogous to those which the body may suffer from injuries after birth. But these various lesions are complicated in the embryo by the fact that it is in a state of active growth and development, so that even slight injuries may result in malformations of the most extreme character, especially when inflicted in the earlier periods of its life.

Among the abnormal and harmful conditions to which the embryo may be subjected may be mentioned first those which relate to the mother, such as infectious or other diseases, disturbances of nutrition, severe psychic shocks, etc. To these may be added local interference with development, such as pressure upon the uterus, circulatory and other disturbances of the placenta and membranes, an abnormal accumulation of amniotic fluid, adhesions between the embryo and the membranes of the placenta, and various forms of trauma.

On the other hand, there are many abnormalities in development which must be referred back to inherited defects transmitted through the maternal or paternal cells.

While one may catalogue in a general way many of the conditions leading to malformations, the rationale of the process in many instances is still obscure. In recent times much light has been thrown on the subject by a host of experimental studies on the ova of the lower animals by shaking, dissection, and other mechanical interferences. But into this field the scope of this book does not permit us to enter.

Many malformations are so extreme or involve such vital organs that extrauterine life is impossible. Such are some of the malformations

[1] The reader is referred for details to *Thoma*, Pathology and Pathological Anatomy, English translation (bibl.), or to other special works, such as *Marchand*, Missbildungen, in Eulenburg's Real Encylopädie der gesammten Heilkunde, 3d ed., Vienna, 1897, xv, 506; *Schwalbe*, Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, 1906 to 1913; *Ballantyne*, Manual of Antenatal Pathology, 1902 and 1904; and *Rabaud*, La tératogenèse, Paris, 1914.

For a discussion of the embryological side, see *Broman*, Normale and abnorme Entwicklung des Menschen, Wiesbaden, 1911. For a study of tissue displacements during embryonic life, see *Meyer, R.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1905, ix², 518 (bibl.).

of the nervous system or of the circulatory apparatus, occlusions of the gastrointestinal canal, etc. Some of the abnormalities of development, on the other hand, while not fatal, predispose to disease. Such are the embryonal displacements of groups of cells which predispose to tumor formation. It is customary to speak of the lesser defects as congenital anomalies. Such are congenital angiomata, nævi, and certain dermoid cysts.

Malformations may involve a single individual or embryo or they may concern two or more, which are variously united.

Malformations Involving Single Individuals.[1]

The types of such malformations are various. Thus, there may be a failure to develop a part or organ. This is called *aplasia* or *agenesia*. For example, the upper or lower extremities may be absent (Fig. 184).

Fig. 184.—Abrachius. The arms are absent.

When an organ or part is formed, but remains small or undeveloped, we speak of *hypoplasia*. A common example of this is the hypoplasia of the aorta in status lymphaticus (see page 500).

Sometimes a part of the body remains at an early developmental stage; under these conditions, however, the developmental arrest may not involve cessation of growth. Examples of this form of lesion are the various fissures and clefts which occur in the median line or other parts of the body, due to some interference with the closure of the invaginations of the germinal layers which should take place at an early fetal period—the medullary groove, intestinal groove, facial and branchial clefts.

From fissures in the facial region arise such malformations as absence of the whole or parts of the face (Fig. 185 and 443), various forms of harelip (Fig. 186), etc. Defects of closure in the cervical and thoracic region lead to many forms of fissures, fistulæ, cysts, etc., of the neck and chest, such as the branchial cysts, branchial fistulæ, auricular appendages, and tracheal fistulæ. The lower jaw may be absent (*agnathia*). Under these conditions the mouth may be represented by a small opening and the ears may be placed low down and near the median line (*synotia*)

[1] Many of the developmental defects occurring in a single fetus are considered somewhat more in detail in the part of this work dealing with the special organs, to which the reader is referred.

FIG. 185.—FACIAL FISSURE.
Owing to imperfect union in the anterior median line of the body, in the facial region the larger irregular cleft persists. There is also absence of the vault of the skull—cranioschisis.

FIG. 186.—DOUBLE HARELIP.
There is bilateral fissure extending into the hard palate.

(Fig. 187). There may be fissure of the sternum, sometimes with protrusion of the thoracic viscera, among others the heart—*ectopia cardis*. Fissure of the diaphragm may occur with that of the sternum and permit displacement of the abdominal and thoracic viscera. The imperfect closure of the *abdominal wall* leads to various forms of lesions. Thus

FIG. 187.—SYNOPHTHALMIA, AGNATHIA, AND SYNOTIA.
The rudiments of two eyes are fused and occupy a common orbit—synophthalmia. A wart-like process lies above the orbit. The lower jaw is absent—agnathia. The mouth is small. The ears are low and near the middle line between the upper jaw and the neck—synotia.

there may be a patent urachus, the formation of a *Meckel's diverticulum* (see page 769), umbilical hernia, or, when there is large deficiency of the abdominal wall—complete abdominal fissure—there may be prolapse of the abdominal viscera (Fig. 188). Fissure of the lower portion of the abdominal wall may lead to prolapse of the bladder, and the bladder itself may be fissured so that the interior of the prolapsed organ is

exposed—*inversio vesicæ*. Such fissures in the anterior median line may involve the urethra, leading to *epispadias* or *hypospadias*.

A failure of the walls of the medullary groove in the posterior median line of the body to fuse properly leads to significant malformations of the central nervous system. This failure may be complete—*craniorrhachischisis totalis* (Fig. 189). There is a wide irregular groove involving the dorsal aspect of the head and trunk. In this condition, however,

FIG. 188.—ABDOMINAL FISSURE.
Prolapse of the abdominal viscera through imperfect closure of abdominal wall.

the anterior portions of the brain, with the nose and eyes, may be formed, though distorted.

But there may be only a partial failure in the closure of the medullary groove, limited to longer or shorter segments, especially in the cervical and sacral regions. Thus arise various forms of *myelomeningocele*, in which the pressure from within not being sustained by vertebral arches, the skin and underlying soft parts are often forced outward in the form of a pouch or sac (Fig. 190).

A local failure in the closure of the anterior portion of the medullary groove may lead to many malformations of the skull—*cranioschisis*, *hemicephalia*, *acrania*—and to various forms of *meningocele*; thus in

fissures of the skull there may be prolapse of parts of the brain and its membranes, forming with the inclosing skin pendent pouches of various forms—*encephalomeningocele* (Fig. 191). The vault of the skull may be absent, and on the base there may be small amounts of brain substance, or this may be entirely absent—*anencephalia* (Fig. 192). For the details of some of these lesions we must refer to the chapter on the Nervous System and to special works on malformations.

In many of the developmental lesions of the brain, the anterior parts, especially the optic vesicles and the olfactory bulbs, are often

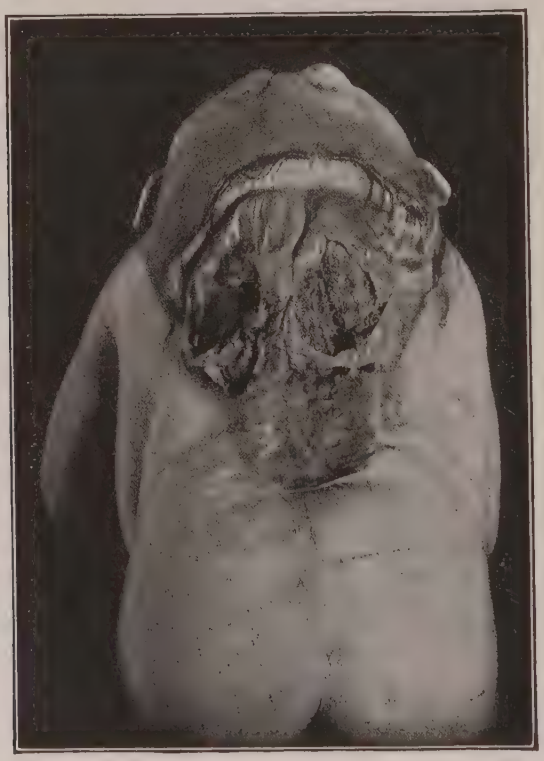


Fig. 189.—Craniorrhachischisis.
A failure of the medullary groove to close along a portion of the posterior median line.

but little affected. But we may note here one of the striking malt formations which results in the fusing of the eyes into one placed in the forehead near the median line. This condition is called *synophthalmia* or *cyclopia* (see page 1132).

Finally, there may be an arrest of development, more or less complete, of the brain or some of its parts—*micrencephalia*.

In one phase of malformation involving single individuals, paired organs may be grown together, for example in the so-called "*horse-*

shoe kidney" (Fig. 193). Or single organs may retain lobular forms belonging to an early period of life—*lobulated kidney.*

There may be supernumerary parts, such as fingers, toes, etc., or organs—spleen, adrenals, lungs, pancreas. There may be fusion of fingers and toes, frequently involving all of the extremities. Various congenital malformations commonly due to arrest of development are exemplified in the diverse phases of "club-foot"—*talipes*—and "club-hand"—*talipomanus.*

Fetal structures which in the normal development should make way

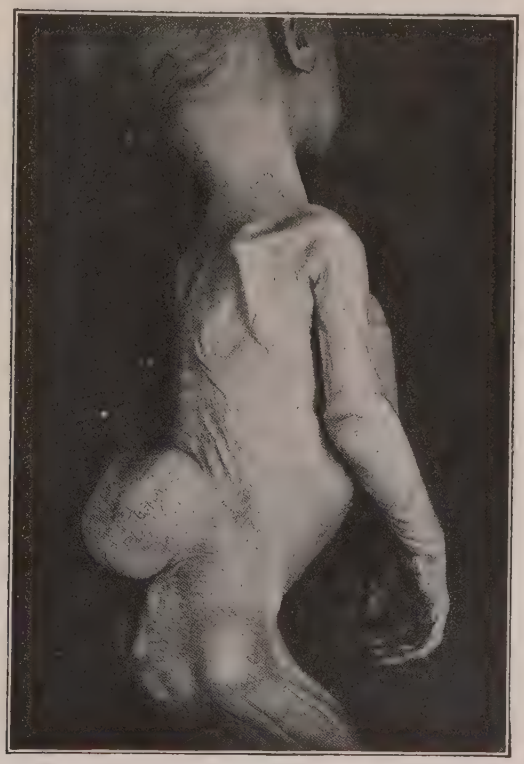


FIG. 190.—MYELOMENINGOCELE SACRALIS—SPINA BIFIDA.
From a partial failure in the closure of the medullary groove this sac is formed, containing fluid and the lower portion of the spinal cord.

for adult organs may persist; thus the urachus, the Wolffian ducts, or, parts of the branchial clefts, may remain.

Through adhesions of the membranes or by abnormal winding of the umbilical cord about the neck or the extremities (Fig. 194), partial decapitation or amputation of a limb may take place (Fig. 195). So also by adhesions of the surface of the embryo and the placenta or the membranes, various disturbances of growth may occur.

Normal and Pathological Conditions in which Two or More Individuals Develop Together.

Two or more individuals may develop together, the bodies being separated, as in normal twins, triplets, etc., or the individuals being more or less closely joined or merged. This duplication may be evident, so that the nature of the complexity is clear; or one of the individuals may develop greatly in excess of the other.

FIG. 191.—ENCEPHALOCELE.
There is a fissure on the posterior aspect of the skull, out of which the imperfect brain and its membranes protrude, filling the pouch of the scalp.

Twins, Triplets, etc.—Pregnancies may be complicated by the development in the uterus of two or more embryos. These are called twins, triplets, etc. This duplication may arise by the development of separate ova or the formation of more than one embryo from one ovum.[1]

Twins and triplets developed from one ovum—homologous twins—are always of the same sex; and if both develop normally they usually

[1] See *Newman, H. H.*, Biology of Twins, Chicago, 1917.

closely resemble each other. But the individuals, if born alive, often do not develop equally; one may be less well nourished than the other, from a disturbance of the vascular supply, for example.

One of the twins may die early in pregnancy and suffer varying degrees of degeneration into a shapeless mass, or may die later and be born prematurely or at the delivery of the living twin (Fig. 196). Some of these abortive forms are without a heart or have only a rudiment of that organ. These are called acardiac monsters (*fetus acardiacus*). They may consist of connective tissue, rudimentary bones, and portions of intestine, and be covered by skin with hair—*acardiacus amorphus.* Or there may be a more or less distinctly formed head without a corresponding trunk—*acardiacus acormus.* There may be a fairly well developed trunk with viscera and a rudimentary heart, but no head—*acardiacus acephalus.* Finally, there may be a relatively well developed trunk with defective extremities and a rudimentary heart—*acardiacus anceps.*

FIG. 192.—CRANIOSCHISIS.
The vault of the cranium is absent. There is a small reddish mass at the base representing the rudiment of a brain.

In all of the above duplications the fusion is confined to the placenta and its appendages, the bodies of the twins being separate.

Double Monsters (Monstra duplicia).—The union to any considerable extent of the embryos themselves is pathological, and the malformations are classified as double monsters.

In these unions of twins there may be: 1, complete duplication of the axis of the germinal area, so that there is a double development of the central nervous system, while the remaining parts are more or

less fused; or, 2, there may be only a partial duplication of the axis, so that there may be double development, either of the head or in the sacral region, while at the other extremity the body is single.

We shall now look briefly at some of the forms of double monsters in which the individuals are more or less symmetrically united.

There may be fusion of the bodies in the thoracic region. The ensiform processes are united by cartilage, union of the soft parts extending over the umbilical region. The thoracic and abdominal cavities

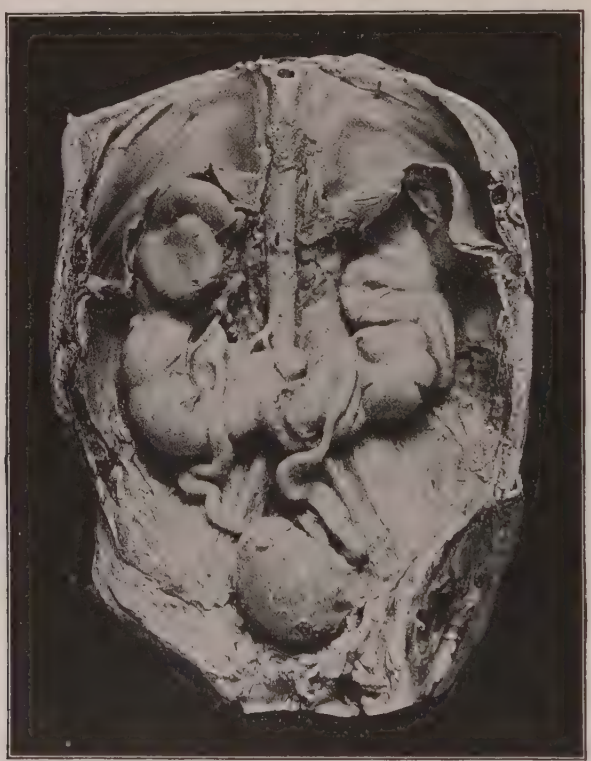


FIG. 193.—HORSESHOE KIDNEY.
The kidneys are in place in the body of the young child. They are lobulated with the large adrenals above them.

are separate. This malformation is called *xiphopagus*. Such were the celebrated Siamese twins who lived to the age of sixty-three. In other cases there is a common thoracic cavity, usually with two hearts and two pairs of lungs more or less malformed (Fig. 197 and Fig. 198). The abdominal cavities may also be united. Parts of the intestine may be common to both twins. These monsters are called *thoracopagus*. They do not long survive birth. The fusion may, however, extend

upward so that two upper extremities may fuse—*thoracopagus tribrachius;* or two of the lower extremities may fuse—*thoracopagus tripus;* or, finally, the fusion may embrace the head so that the faces are more or less united—*prosopothoracopagus.* The cephalic and thoracic regions may remain separate while fusion takes place from the umbilicus to the pelvic region. The spinal column is duplicated while there is a common pelvic ring—*ischiopagus.*

There may be fusion of the otherwise separate twins in the cranial

Fig. 194.—Fetus with Umbilical Cord Coiled Around the Neck and Leg.

region—*craniopagus.* The union is usually only of the scalp and cranial bones.

The head and the upper part of the body may be single, or the head alone may be single while the abdomen and pelvis are separate. There may be four or less lower extremities. Such malformations are called *dipygi.*

There may be union of the head, neck, or chest, so that there are two faces more or less symmetrical looking in opposite directions—*janiceps* or *janus.*

In cases in which there is only a partial duplication of the axis, this may be most marked at the cephalic or caudal extremity, and there may be formed an individual with duplication of the face—*diprosopus*. Thus, depending upon the degree of duplication, arise *diprosopus distomus; d. diophthalmus; d. triophthalmus; d. tetraophthalmus*. But this anterior duplication may extend to the whole head. Thus arise the two-headed monsters—*dicephalus*—which according to the degree of duplication

Fig. 195.—Partial Intrauterine Amputation of the Leg.

of the upper extremities are called *dicephalus tribrachius; dicephalus tetrabrachius*.

Finally, the bodies are united posteriorly in the region of the sacrum and coccyx. This malformation is called *pygopagus*. The individuals may live for years.

In the double malformations which we have thus far considered there has been a more or less symmetrical development of the physically joined twins. But for various reasons it often happens that one of the individuals is arrested in its development, while the other continues. This condition is analogous with that already considered in which the

arrest of development involved an independent acardiac individual which was not viable. But in the present case the arrested twin is joined to the other as a part of a living organism, and its life is thus maintained by the more favored relative. Under these conditions the more completely developed twin is called the *autosite*, the arrested embryo, the *parasite* (Fig. 199).

The rudimentary structure, the *parasite*, may be variously developed. It may have extremities, various forms of tissue, nerve, muscle, intestine,

FIG. 196.—TWINS.
The individuals are separate. One died early *in utero* and is only partially developed and mummified.

etc. It may be formed of a jumble of tissues with cystic cavities which may be lined with epithelium. Its size varies; it may be as large as the body of the autosite. Thus may be formed the *parasitic thoracopagus*, attached to the sternum, or the *parasitic ischiopagus* and *parasitic craniopagus*. So also are formed the *epignathus*, in which an acardiac parasitic rudiment is attached to the autosite in the facial region. The rudimentary embryo may be attached in the sacral region, forming sacral appendages or tumors—*sacral teratomata*.

Finally, the second individual may be much less developed than in the cases which we have thus far surveyed, and may be represented only by formless appendages or by inclusions in different parts of the body, which are made up of various and often complex tissues—fibrous tissue, nerve tissue, bone, teeth, cartilage, muscle, glands. These are

FIG. 197.—THORACOPAGUS.

called *teratoids*, *dermoids*, *fetal inclusions*, *congenital teratomata*. They may occur in the ovaries, or testicles, or about the head, in the mediastinum, or in the sacral region, and elsewhere. They often become cystic and may give origin to various forms of tumors (see page 1134).

The teratomata are apparently derived either from extruded polar

bodies or, more probably, from blastomeres segregated at an early period from the cell complex which goes to form the developing fetus. The separated cells may long remain latent, finally beginning to grow with the power to form complex tissues and structures, but only in a jumbled mass, embraced within or attached to the developed individual. Some of the teratomata are comparatively simple in structure. Their nature

Fig. 198.—Skeleton of Thoracopagus—Pig.

is often revealed by the heterologous character of their component structures. The ectodermal elements are often most conspicuous (see page 403).

We thus see, in summary of this brief survey of complex malformations in general, that under normal conditions two or more individuals may develop together in the uterus—twins, triplets, etc. Under pathological conditions the individuals may be more or less united, forming

double monsters. The duplex individuals may develop more or less symmetrically with independent cerebrospinal axes and various degrees of union. Or the development may be very unequal, so that one is a more or less obvious appendage to the other. Finally, one of the individuals may exist as a mere complex rudiment attached to or within its more favored mate.

FIG. 199.—CHILD WITH ACARDIAC PARASITE ATTACHED POSTERIORLY. One of the twins, the autosite, has developed; the other only partially.

TISSUE MALFORMATIONS

While there is but little question as to the nature of the conditions underlying the formation of united twins or even of the complex parasitic attachment of a partially developed twin to a normal fetus, there has been much doubt cast upon the possibility of the persistence of embryologically displaced fragments of tissue, the hypothesis upon which Cohnheim years ago based his theory of tumor development. Nevertheless, investigations of recent years have thrown much light on the theory that inclusions of cell complexes derived from early embryonic existence may remain in various portions of the body. Some of the most striking examples of the persistence of fragments of organs are offered in the minute study of the urogenital system of the female, where the very complexity of the organ development makes it possible that cells or groups of cells may be left behind in the course of the wanderings of the organs to their

final position.[1] In the literature of the subject a large number of definite observations now exist concerning the persistence of the Wolffian or Gartner's ducts. The presence of glandular structures from these ducts and fragments of adrenal tissue has been frequently noted in the round ligament. Analogous displacements are observed of the pancreas, fragments of which are not uncommon in the stomach wall, duodenum, mesentery, and Meckel's diverticulum. Fragments of thyroid tissue are found at the base of the tongue and along the thyreoglossal duct. Epithelium, both squamous and cylindrical, is not infrequent as remnants of the branchial clefts, and may remain as epidermoid cysts about the embryonic suture lines of the face. Fragments of the adrenal have been found in the kidney and liver, retroperitoneally, in the broad ligament and, as just mentioned, in the round ligament of the uterus. Such well characterized structures, however, are more easily identified than a few displaced cells of the connective-tissue group, but the study of complex tumors, especially those of the parotid region, the kidney, uterus, and other organs, has led to the belief that even a few cells may be displaced and remain viable throughout adult life. Such cells are only accidentally found—striated muscle, for example, has been discovered in a normal uterus—and, as a rule, they make their presence felt only when they undergo the necessary biological alterations which result in their obtaining an enhanced proliferative power, in other words become the basis for tumor formation. The theory of cell misplacements, therefore, seems to be the best explanation of many of the complex tumors. For example, the parotid tumors, in which striated muscle, cartilage, bone, and squamous epithelium are present, besides a host of other tissues, both epidermal and mesodermal, are best interpreted as misplaced fragments of highly potent embryonic tissue deposited during an early period of development while the gland was as yet imperfectly formed. So, too, the complex tumors of the kidney, which contain cartilage, striated muscle, and remnants of embryonic kidney structures, must be interpreted in this way rather than by having recourse to a broad theory of metaplasia, which by breaking down all histological boundaries really explains nothing but merely avoids the problem. For if connective tissue can be turned into striated muscle, it can be pertinently asked of those who believe in metaplasia why such transformation occurs practically only in such portions of the body as the face, kidney region, and genitourinary tract, where embryological development is of the utmost complexity. The same explanation must be offered for a certain portion of the complex tumors developing in the region of the postanal gut, described in a preceding paragraph. The still more elaborate teratomata of the ovary and testicle do not belong in this group but are probably derived from cells separated from the ovum at so early a date that they retain an histological totipotence.

[1] For an interesting collection of inclusions of embryonic tissue, especially in the female genital tract, see *Meyer, R.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1911, xv[1], 430 (bibl.).

Herxheimer, G., Missbildungen des Herzens und der grossen Gefässe, Schwalbe, Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, 1910, iii, iii, Lieferung, 339, ibid., Die Einzelmissbildungen, 1913, iii, x, Lieferung, 51.

CHAPTER XI

TUMORS

General Nature

The word *tumor*, originally applied by ancient Greek and Roman writers to any swelling, has with the increase in our knowledge in modern times become more and more restricted in its use, until it is now employed only to designate more or less circumscribed growths of new tissues, or neoplasms. But as the formation of such new tissue is of common occurrence under both normal and abnormal conditions it is desirable to fix upon some features by which true tumors may be distinguished from other tissue growth, either normal or abnormal.

A tumor, like any other tissue, is produced by the proliferation of cells originally of a normal type. During the course of such growth, the cells may assume considerable variations from the normal, and finally be only with difficulty recognizable as belonging to the group of cells from which they sprang; but the definite plan to which all normal cells in the body adhere and by which the good of the organism as a whole is assured, appears, in the case of a neoplasm, to be abandoned. The cells, in other words, have ceased to be functionally important to the body. Thus, under normal conditions, epithelium, for example, is constantly replaced to compensate for the losses which it daily undergoes, and even the formation of large masses of new tissue may occur under some special etiological stimulus, as in the lactating mammary gland and the uterus during the course of pregnancy, but under such circumstances, even in abnormal conditions, like inflammation, the end obtained is for the good of the organism as a whole; no more new tissue than the required amount is produced, nor is more than is actually required elaborated, as in the case of a bone callus; the surplus is usually absorbed with comparative rapidity. This is not true for neoplasms. They are characterized in general by such independence, both in structure and in growth, of those laws which govern the body topography that their distinguishing characteristics are best indicated by the word autonomy, or perhaps by a stronger term, cell anarchy. The autonomous character of tumor tissue, manifested primarily by its independent growth, is evident also in its tendency to vary in structural type, in the functional aberration of the cells, and in the ability of these cells to multiply after transportation into another part of the host's body, or even after grafting into the body of another individual, as in the case of artificial transplantation of a malignant tumor from one animal to another. Thus a tumor represents an independent group of cells whose only dependence upon the host's body

lies in the fact that the general blood supply is levied upon for its nutrition. An excellent example of the disregard shown by tumors for the general laws of morphology and nutrition[1] is seen in lipomata, tumors composed of fat cells, where a large growth may persist and even expand in size in a poorly nourished individual whose body fat has otherwise practically disappeared.[2] While this independence is a striking characteristic of certain tumors, there are others in which it is not so prominent, and it is even impossible, in some instances, to distinguish between tumors and other newly formed tissue chiefly because we do not yet possess definite criteria for a distinction in all instances between normally growing cells and those of tumors.

Definition.—The most generally accepted definition of a tumor is that it is a tissue overgrowth which is independent of the laws governing the remainder of the body. It is usual to add as a qualifying phrase to separate tumors from reparative processes, such as bone callus, that the neoplasm serves no useful purpose to the organism. The fact that in extremely rare instances tumors may secrete the hormones characteristic of the gland from which they spring does not in the least weaken the value of this portion of the definition, for even while a thyroid neoplasm may be secreting the hormone which prevents the development of myxedema, the tumor itself is at the same time destroying the life of its host; therefore its functional capacity is only accidental and atavistic and can hardly be considered as disproving the statement that a tumor serves no useful purpose.

Continuous growth is also frequently added to the definition of a tumor, but this must be eliminated because although the great majority of tumors do proliferate indefinitely at least during the life of the host, even a highly malignant neoplasm may under very exceptional circumstances undergo partial or complete regression. This extremely unusual outcome is most often encountered among the chorionepitheliomata but has been observed in many other types.[3] Furthermore the successful cultivation of embryonal connective tissue *in vitro* for a period of ten years[4] shows that these cells also are capable of unlimited proliferation under suitable circumstances, and it is also certain that this type of cell grows much more luxuriously under these conditions than does the cancer cell, or the adult normal cell. Thus the faculty of endless growth is characteristic not only of neoplasms but also of normal somatic tissues when a proper environment is assured.

Structure.—While tumors in general are composed of the same varieties of tissues as those normally existing in the body, occasional exceptions are found in those neoplasms of complex types derived from congenitally displaced tissue. In such instances, for example, myxomatous tissue or similar structures, not normally found in the adult body, may be present

[1] For a discussion of diet and tumor growth, see *Rous*, Jour. Exper. Med., 1914, xx, 433; *Woglom*, ibid., 1915, xxii, 766; and Drummond, Biochem. Jour., 1917, xi, 325.

[2] *Hirsch, E. F.*, and *Wells, H. G.*, Retroperitoneal liposarcoma: report of an unusually large specimen, with chemical analysis, Amer. Jour. Med. Sci., 1920, clix, 356.

[3] *Rohdenburg*, Jour. Cancer Res., 1918, iii, 193.

[4] *Ebeling, A. N.*, A Ten Year Old Strain of Fibroblasts, Jour. Exp. Med., 1922, xxxv. 755.

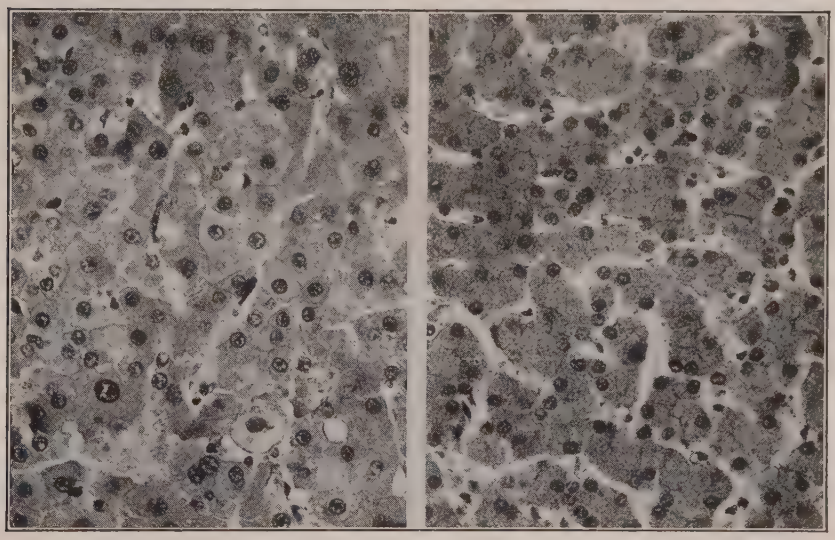
in the tumor. Exceptions like this, however, are infrequent, and most of the tumors found in the body are derived from preexisting cells of normal type; tumors of the connective-tissue group arising from connective tissue elements, while those of the epithelial variety arise from epithelium, and so on. Most of the primary tumors originate from structures normal to the site where they grow, and are therefore said to be autochthonous in contrast to those forms arising from congenital displacements of tissue which are termed heterochthonous, or in simple English, native and foreign. An example of the former is seen in the adrenal tumors arising in the suprarenal body; of the latter in growths of undoubted adrenal tissue occasionally seen in the broad ligament or liver. While in general the tumor cells resemble more or less closely those from which they are derived, the statement has been repeatedly made and is even now current that the cells of malignant tumors, and particularly of the carcinomata, have a characteristic structure and appearance, and that by the examination of single cells the nature of the tumor can be determined. Inasmuch, however, as all the cells of the neoplasm have their source in cells of the normal body, with the exception of the congenital group named, there is nothing wholly characteristic in the appearance of a single element of the tumor, it is only by the study of the general relationship and distribution of cells, and very rarely by the examination of the characters of the individual cells themselves that we are able to determine the nature of a tumor. In an occasional instance it is necessary to know something concerning the site of origin of the tumor and the clinical history before a definite conclusion can be reached.

While the cellular morphology and the histological topography of different organs are closely dependent upon factors such as mechanical pressure, nutritive conditions, relationship to surrounding parts, state of secretionary activity of cells, and so on, under the circumstances in which tumors develop, however, these influences may be disturbed so that the shape, size, structure and the mutual relationship of the cells of the tumor, their tissue organizations, and their various functional characteristics as reflected in their morphology may be more or less profoundly modified. There are also changes in the cells of tumors which have been designated anaplasia,[1] a term designating the loss of a characteristic differentiation which the adult cells undergo. While as has been said the tumor cells usually imitate the appearance of those of the structures in which they originate, they nearly always fall short of wholly reproducing the normal morphology in both histology and function. The cells in other words are immature, or poorly developed, being generally less highly differentiated than the corresponding mature normal cell. This stage is occasionally designated as a return to the embryonic type, but there is no evidence that biologically these cells are really related to the cells of the embryo, or that the analogy of an atavistic return to embryonic qualities is in any way valid. The departure from type may be so slight that even with a malignant tumor it may not be possible to determine the true nature of the growth, except for the fact that metastatic nodules are found at

[1] *v. Hansemann*, Berl. klin. Wchnschr., 1909, xliv, 1850.

some distance from the primary growth (Fig. 200). This however, is a very exceptional circumstance, and usually there is a sufficient differentiation to permit of determination of the nature of the tumor.

In our present state of knowledge concerning the biology of cells of tumors, it is well to avoid terms such as embryonal in describing the cells of a neoplasm, lest the idea be unconsciously adopted that the cells thus described have regressed to their embryonal state. For this assumption there is no evidence in fact,[1] and it is probable that the elements of a malignant tumor appear immature only because of the conditions under which they live and the rapidity of multiplication which they undergo.



A *B*

FIG. 200*A*.—SECTION OF A LUNG METASTASIS FROM A CARCINOMA OF THE LIVER. MAGNIFIED 250 DIAMETERS.

FIG. 200*B*.—SECTION OF A LIVER WITH A LITTLE CHRONIC CONGESTION, OTHERWISE A NORMAL ORGAN. MAGNIFIED 250 DIAMETERS.

It will be noticed in the tumor that the liver cells are closely packed together and there are none of the sinusoids between the trabeculæ as there are in the normal liver. The fixation of the two specimens is slightly different also, so that the cells in the liver section are more granular than those in the tumor. The very slight difference between the cells of the tumor and the normal organ is evident at a glance.

On the other hand, there is no objection to the terms "mature" and "immature," and "differentiated" and "undifferentiated," as applied to cells or tumors. They may be assumed to be purely descriptive, and not imply anything concerning the biology of the cells themselves.

The tissues of tumors may be divided into two portions, a characteristic, usually the more rapidly growing fraction, the parenchyma, and a non-specific comparatively inert connective tissue portion, the stroma, which supports the parenchyma, and carries blood vessels for its nutrition. In the carcinomata the stroma is derived from the normal connec-

[1] See for a discussion of this question based on a study of the ferment content of embryonal and tumor cells, *Buxton* and *Shaffer*, Jour. Med. Res., 1904–05, N. S. viii, 543.

tive tissue of the organ in which the tumor arises. Its quantity seems to depend somewhat upon the nature of the tumor. The epithelial cells of some forms seem to stimulate the surrounding connective tissue to active growth, and thus, in the long run, the number of epithelial cells may be small in proportion to the connective tissue stroma. On the other hand, tumors composed almost entirely of epithelial cells with a minimal amount of stroma are not infrequent. The same conditions apply to the number and nature of the invading wandering cells, some tumors seeming to incite the appearance of large numbers of plasma cells or lymphocytes;[1] the stroma of others contains vast quantities of eosinophiles,[2] while in still other forms neither of these wandering cell types is present in large quantities. In some sarcomata the bulk of the stroma may be so great that it determines all of the physical qualities of the tumor, and a differentiation, even by the microscope, from a fibroma may be impossible, while in other types the stroma may be extremely scanty or almost non-existent as, for example, in the lymphosarcomata. In the angiosarcomata, the stroma is largely composed of blood vessels, which give rise to the characteristic gross appearance and microscopic morphology of the neoplasm. In certain of the sarcomata arising from bone the stroma may be of an extremely variable nature. It may contain osteoid and cartilaginous material as well as blood vessels and connective tissue cells. In the sarcomata therefore the stroma may or may not play an important part in determining the growth and microscopic characteristics of the neoplasm.

Functionally the only relation between a tumor and the stroma of the host is through the blood vessels. Lymph-vessels are scanty or absent from tumor tissue. Nerve fibers also are usually absent, or very scanty, those present being filaments left during the invasion of the normal structures.

Terminology.—It is customary to terminate the name of a neoplasm with the suffix "oma;" this is preceded in most cases by the name of the tissue in which the tumor has originated—as *myoma*, a tumor originating in muscle; *glioma*, one developing from the glia, etc. The nomenclature, however, is badly in need of revision; thus the *cylindroma* was called by this term on account of the hyaline cylindrical structures which it contains, while the *psammoma* received its name from the Greek for sand, because of the small gritty particles scattered through it.

It will be noted that neoplasms are named from the *tissue*—not the *organ*—involved. Hence, the use of such appellations as *hypernephroma* (a tumor of the adrenal), *thymoma* (a tumor of the thymus),[3] *hepatoma* (a tumor of the liver),[4] is to be discouraged.

In the names of neoplasms containing more than one kind of tissue, the principal constituent is placed last. An *osteochondroma*, accordingly,

[1] *Da Fano*, Ztschr. f. Immunitätsforsch. u. exper. Therap., Orig., 1910, v, 1.
[2] *Fischer, W.*, Zieglers Beitr., 1913, lx, 1.
[3] *Grandhomme*, Über Tumoren des vorderen Mediastinums, Darmstadt, 1900; *Thiroloix* and *Debré*, Arch. de méd. expér., 1907, xix, 668; *Simmonds, M.*, Ztschr. f. Krebsforsch., 1913, xxi, 280; *Ewing*, Surg., Gynec., and Obst., 1916, xxii, 461.
[4] *L'Esperance, E.*, Jour. Med. Research, 1915, N. S. xxvii, 225.

is a *chondroma* containing some bone, while a *chondroosteoma* is an osteoma containing some cartilage.

Degenerative Processes in Tumors.—Tumors are subject to the same degenerative changes as are other tissues. They often undergo degeneration from failure on the part of their blood supply to keep pace with the rapidly increasing demands upon it, or by themselves shutting off mechanically, as they increase in size, a supply which might otherwise be sufficient; again, circulation may be restricted in a pedunculated tumor by torsion of its pedicle. The results of this deprivation soon become evident in the form of fatty or other degenerations, calcification, ulceration, gangrene, etc. Indeed, a neoplasm may be largely destroyed in such a way.

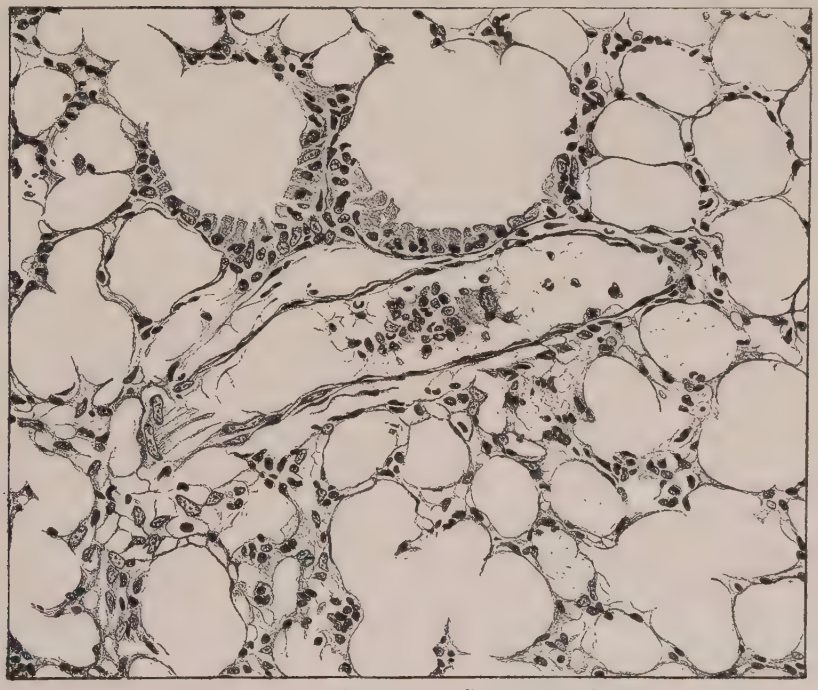


Fig. 201.—Tumor Embolus in Capillary of Lung.

Benignancy and Malignancy.—A benign tumor proliferates slowly by *expansive* or *central* growths. A malignant neoplasm, on the other hand, attacks and replaces the surrounding tissues, spreading by *infiltrative* or *peripheral* growth. Benign tumors do not metastasize, as a rule, nor do they recur after removal.

The three main attributes ordinarily ascribed to malignancy are: *Infiltration* of the surrounding tissue, *metastasis*, and *recurrence* after removal. Still, *infiltrative growth* is not entirely characteristic of the malignant tumors, since the cells of the normal placenta have this property, invading the uterine wall and its blood-vessels, and sometimes actually reaching the lungs in the form of emboli; and the hemangioma,

ordinarily a benign tumor, grows nevertheless by infiltration.[1] Developing glands in the embryo are also able to invade subjacent tissues, although here, as in normal placentation, the process finally comes to an end; in malignant growth, on the contrary, it continues with but very few exceptions until the death of the patient has been brought about.

Metastasis, or the development of secondary nodules in either proximate or remote portions of the body, is a consequence of the transplantation of tumor cells through the blood-vessels (Fig. 201 and 202) and lymphatics, and their growth at the point where they come to rest. Not all tumor cells reaching the circulation, however, survive long enough to produce secondary tumors.[2] The migrating cells usually travel in the direction of the current, although in the lymphatics they are occasionally able to make their way against it (*retrograde metastasis*). Metastasis may occur, also, *by contact*,[3] as when cells from a tumor on the lower lip are transplanted into the upper and give rise to a tumor at the latter site. Some of the recorded cases, however, may have been instances of multiple tumor or of retrograde metastasis.[4]

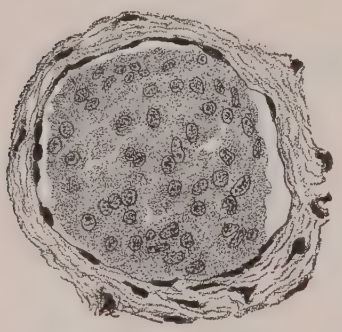


FIG. 202.—A TUMOR-CELL EMBOLUS GROWING IN A BLOOD-VESSEL AT A DISTANCE FROM THE PRIMARY CARCINOMA IN THE MAMMA.

The way in which metastatic nodules develop offers a powerful argument against the parasitic hypothesis of tumor genesis. In every infectious disease with which we are acquainted, the local manifestations are produced by a tissue reaction directed against the invading microorganism; thus, the cells of a pulmonary tubercle are derived from the lung itself, those of an hepatic tubercle from cells of the liver, etc. The situation is entirely different, however, in secondary tumors, the parenchyma of which is produced solely by the proliferation of cells transported from the primary growth.[5] Accordingly, a metastasis in the lung from a mammary carcinoma, say, is composed, not of pulmonary elements, but of cells from the mammary gland, the only portion contributed by the lung being the stroma. But not only are daughter tumors made up of cells from the primary growth; they even reproduce more or less the architecture of the parent neoplasm, so that metastases from an adenocarcinoma of the stomach appear as adenocarcinomata, while those from an epithelioma reflect the structure of the skin. Even the physiological task of the parent organ is undertaken, as when cerebral metastases from an hepatic growth discolor the surrounding brain with the bile which they secrete.

[1] *Borrmann*, Zieglers Beitr., 1907, xl, 372; *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 208.

[2] *Schmidt*, Die Verbreitungswege der Karzinome, Jena, 1903; *Brasche*, Virchows Arch., 1914, ccxv, 106.

[3] For a review of the subject, see *Woglom*, The Study of Experimental Cancer, New York, 1913, p. 44.

[4] *Petersen*, Arch. f. Dermat. u. Syph., 1904, lxx, 313; *Tendeloo*, München. med. Wchnschr., 1904, li, 537.

[5] For experimental verification, see *Jensen*, Centralbl. f. Bakteriol., Orig. I., 1903, xxxiv, 27; *Bashford*, *Murray*, and *Cramer*, Second Sci. Report, Imperial Cancer Research Fund, London, 1905, Part 2, p. 24.

As a general rule, sarcomata metastasize by way of the blood stream and carcinomata through the lymphatic system, although exceptions to these rules are not unknown; therefore, sarcomata usually spread first to the lungs and carcinomata to the adjacent lymph-nodes.

The organs to be involved in metastasis depend in some degree upon the situation of the primary growth. Carcinomata of the stomach and intestine, for example, are apt to metastasize in the liver, those of the prostate in the bones, etc. The fact that any given region offers a site of predilection for secondary tumors can often be explained by the anatomical relationship of the two parts; in other words, it is sometimes largely a matter of simple mechanics, as in the case of the vulnerability of the liver to infection by secondary growths from gastric carcinoma.[1] Again, the spleen, which is commonly described as a soil practically immune to metastasis,[2] proves to be a favorable location, in animals at least, for tumor grafts which have been inoculated into it; whence it appears that its freedom is due more to the failure of tumor cell emboli to lodge in it[3] than to any inherent unsuitability for their proliferation.[4] In many instances, however, the explanation is not so simple; no perfectly definite reason can be advanced to explain why the cells of a prostatic carcinoma should prefer the osseous system, and it is most probable that factors still unknown are in operation, one of which may prove, after all, to be the nature of the soil in which the cells have been sown. At any rate, it is asserted that the occurrence of bone metastases cannot be referred exclusively to the mechanical deposition of tumor emboli, but must depend upon the existence in bone, as such, of conditions favorable to their development. Thus, Schmorl[5] was able to show that metastasis might take place in ossified laryngeal cartilages, while the rest of the body remained free from secondary growths.

When a malignant tumor involves the bone-marrow, either directly or by metastasis, the anemia which results is usually much more severe than the anemia which occurs when such involvement does not take place. Under conditions not yet fully understood, metastases may cause an extraordinary hyperplasia of the marrow with discharge of cells into the circulation, giving a picture suggestive of a myelogenous or lymphatic leukemia or of pernicious anemia. In other instances, an aplastic anemia may be induced through extensive destruction of the marrow by the tumor without causing a corresponding reaction.[6]

Like infiltrative growth, metastasis is not absolutely characteristic of malignancy, since even morphologically benign tumors[7] (chondroma, angioma) sometimes form secondary nodules. See page 413.

The third feature of malignancy, *recurrence* after removal, appears

[1] For a brief review of the question, see *Woglom*, Jour. Exper. Med., 1916, xxiii, 189.
[2] *Chalatow*, Virchows Arch., 1914, ccxvii, 140 (bibl.).
[3] *Kettle*, Jour. Path. and Bacteriol., 1912–13, xvii, 40.
[4] *v. Hansemann*, Deutsch. med. Wchnschr., 1915, xli, 633; *Sappington, S. W.*, Jour. Am. Med. Assoc., 1922, lxxviii, 953.
[5] *Schmorl*, Cited by *Jores:* The Commoner Diseases, Philadelphia, 1915.
[6] See *Wood, F. C.*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917, p. 146.
[7] *Borrmann*, Zieglers Beitr., 1907, xl, 372; *Shennan*, Jour. Path. and Bacteriol., 1914–1915, xix, 139.

only when extirpation has been incomplete. There is no knowing how long tumor cells may persist in the tissues before giving rise to a visible metastasis, but it is certain that in exceptional instances as long a period as ten or even fifteen years may elapse before the recurrence is noticed. Still, this may be regarded as somewhat unusual, and the best surgical judgment inclines to accept five years as the shortest interval which must elapse before cure can be regarded as reasonably assured.

Even recurrence after removal is not typical of malignancy, since such a benign tissue as adenoid vegetations will return unless the operation has been thoroughly performed.

Cachexia is sometimes added as a fourth sign, but it is extremely doubtful whether malignant growths by themselves are able to induce malnutrition; certainly no definite harmful product has ever been demonstrated in their cells. It is much more probable, on the whole, that cachexia is due to the entrance of infection through an ulcerated tumor, to interference with an indispensable organ like the stomach or intestine, or to some influence exerted on the nutrition of the patient by his depressed mental state. So Osler[1] relates that he has known a patient with gastric carcinoma to be relieved of digestive disturbance and to gain eighteen pounds in weight merely as the result of visiting a sanguine consultant who denied the presence of a malignant new growth.

A tumor which is in itself benign sometimes destroys life by pressing upon some vital organ; thus, long-continued pressure by a simple fibroma may cause perforation of an artery, interfere with respiration, block the gastrointestinal tract, etc. In such cases the growth is often said to be *malignant by position*, although it appears better to reserve the term malignant for those neoplasms which possess the three characteristics discussed above; in other words, to regard malignancy purely as a biological and never as an entirely mechanical attribute.

The microscopical evidences of malignancy, while generally unmistakable, are occasionally difficult of interpretation, and even the most expert diagnostician may at times be deceived. This being so, it is necessary for the pathologist to have fragments from different parts of the growth for examination and in particular should he be enabled to investigate the margin where, of course, any invasive tendency will be most clearly shown. But even under the best conditions a decision is reached in some instances only with the greatest difficulty, because no exact criterion of malignancy is yet known.[2] None of the cell inclusions so often described is characteristic of malignancy;[3] and while it is true that the cells and their nuclei are frequently larger in a malignant neoplasm than they are in the corresponding normal tissue, that there is a greater diversity in the shape and size of the cells and in the amount of nuclear chromatin, that the number of mitoses is increased and that they often differ widely from the normal type, it is equally true that all these anomalies may exist in conditions other than malignancy.

[1] *Osler.* Cited by *Weil*, Jour. Am. Med. Assn., 1915, lxiv, 1283.

[2] For a study of mitochondria in tumors, see *Porcelli-Titone*, Zieglers Beitr., 1914, lviii, 237 (bibl)., and *Goodpasture*, Jour. Med. Research, 1918, N. S. xxxiii, 213.

[3] *Greenough, R. B.*, Jour. Med. Research, 1904–1905, N. S. viii, 137.

The individual cells thus offering no certain diagnostic criteria, there remains only the general structure of the growth on which to base an opinion. A tumor of the breast, for example, composed of gland tubules in which all the cells are of approximately equal dimensions and in which each tubule is surrounded by a basement membrane, would be declared benign because it varied but slightly from the normal structure of the organ. Another, made up largely of irregular tubules whose cells varied in size, in staining qualities, and in the dimensions of their nuclei, the epithelium exhibiting in addition to its atypical arrangement a distinct power to invade the surrounding tissues, even though in a few areas only, would be regarded as malignant because of its wide departure from the normal architecture of the breast. Such frank examples as those just cited may be accurately diagnosed in the great majority of cases, although every pathologist encounters from time to time a tumor which,

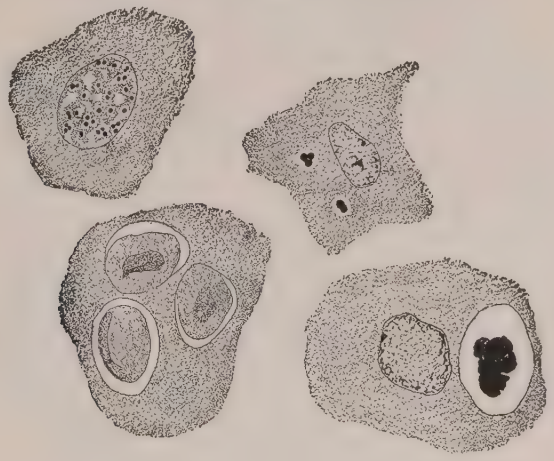


FIG. 203.—EPITHELIAL-CELL AND LEUCOCYTE INCLUSIONS IN TUMOR CELLS.
Such inclusions, which are very frequent in the cells of ulcerating epitheliomata, have in the past been mistaken for intracellular organisms (see also Fig. 204).

in spite of its typical structure, ultimately destroys the patient; and, conversely, a neoplasm of atypical appearance which nevertheless appears to be clinically benign.

It cannot be too strongly emphasized that the natural tendency of a malignant tumor to metastasize is often increased by injudicious examination, because rough or repeated palpation may readily dislodge masses of cells and propel them along the tissue spaces or vessels.[1] Metastasis may perhaps be hastened, also, by cutting into a growth to remove a fragment for microscopical examination, as blood-vessels and lymphatics are opened in the process; clinical opinion, however, is not entirely uniform on this point.[2] That the danger is not entirely imaginary is shown

[1] *Tyzzer*, Jour. Med. Research, 1913, N. S. xxiii, 309; *Knox, L. C.*, Massage and metastases: Ann. Surg., 1922, lxxv, 129.

[2] See *Ewing*, New York Med. Jour., 1915, cii,10; *Greenough*, Med. Record, 1917, xcii, 749; Ann. Surg., 1917, lxvi, 385; and editorials in the Med. Record, 1917, xcii. 728, 1083. For an experimental approach to the question, see *Tyzzer*, Jour. Med. Research, 1913, N. S. xxiii, 309, and *Wood, F. C.*, Diagnostic incision of tumors, Jour. Am. Med. Assoc., 1919, lxxiii, 764.

by the relative frequency with which malignant neoplasms recur in the scar or the suture holes, from cells set free at the time of operation. In view of the prevailing uncertainty it is undoubtedly advisable, whenever possible, to extirpate the entire tumor for diagnosis; but if this be impossible, it would be better practice to remove a portion for examination than to miss the diagnosis entirely.

Etiology.—The development of tumors has been referred, among other causes, to the misplacement and subsequent development of cell groups during embryonal life, to a release with advancing age of the physiological restraint said to be normally imposed upon all the tissues

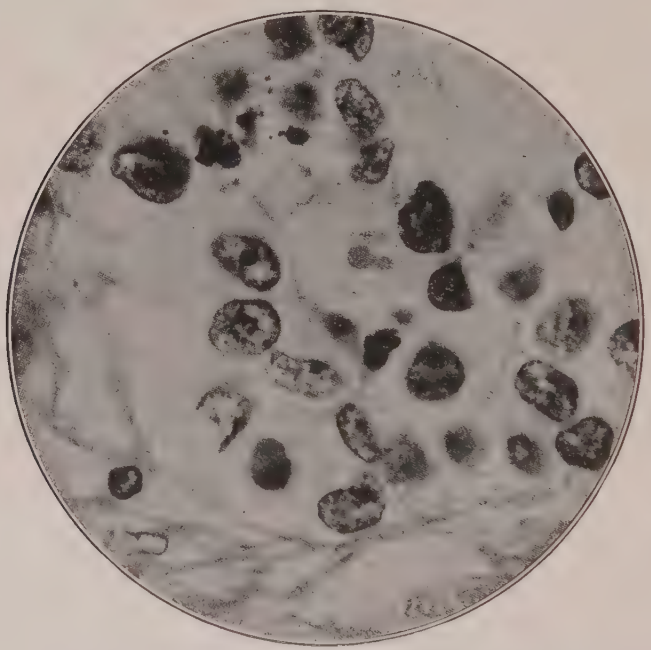


FIG. 204.—PLIMMER'S BODIES IN CARCINOMA OF MAMMA.
These cell inclusions were formerly considered to be parasites; but this view has been abandoned.

of the organism, and to parasites; these are the suggestions which have been most fruitful in provoking discussion and investigation. Of the secondary hypotheses there may be mentioned those that ascribe neoplasia to the development of a specific degeneration and the subsequent emergence of a new cell race; to a loss of function with a concomitant gain in the power of proliferation; to fertilization of the inculpated cells by other elements; to the awakening of "slumbering cells;" to the presence of heterotypical mitoses;[1] to a reproduction of the asexual phase of development (the chorion in mammals and its homologue elsewhere); and to a disturbance of chromosome equilibrium.[2]

[1] *Farmer*, *Moore*, and *Walker*, Proc. Royal Soc., 1903, lxxii, 499. For a refutation of this hypothesis see *Bashford* and *Murray*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 61.
[2] *Boveri*, Zur Frage der Entstehung maligner Tumoren, Jena, 1914.

Most famous of all these hypotheses is the first, which is usually ascribed to Cohnheim,[1] although he was not by any means the first to suggest the association of neoplasms with embryonic rests. In the description of a congenital myosarcoma of the kidney, he suggested that the tumor might have originated in primitive muscle cells separated from the myotome while the foundations of the urinary organs were being laid down, since more cells than are actually necessary may well be produced during early embryonal life; the unutilized elements, it was suggested, undergo isolation at a very early period in their history, and at a time when all their potential power of proliferation remained intact. In the undifferentiated embryonal character of tumor cells, as well as in the early postnatal occurrence of certain neoplasms, Cohnheim sought support for an hypothesis which, he believed, accounted satisfactorily for the variety of tissues so often found in tumors, while at the same time it explained the observation that epithelial growths are most common about the various orifices of the body, the very regions where the embryonal structure is most complicated. Cohnheim made no effort to establish the circumstances which initiate malignant growth in an area of cells separated from the remainder of the embryo in the manner described, though offering the suggestion that one of them might be hyperemia.[2]

This hypothesis has been elaborated by Ribbert,[3] who believes that many carcinomata originate in embryonal remnants, though it is evident enough, he says, that all are not able to assume the malignant type of growth, since many lie indefinitely quiescent. Hence, although embryonal rests possess, in common with other epithelial cell groups, a normal tendency to penetrate underlying connective tissues, these latter structures must under ordinary conditions impose some sort of inhibitory influence preventing attack on the part of the epithelium. A release of the normal invasive power may be accomplished by the presence of inflammation or simple hyperemia in the connective tissues, though it is at once apparent that such lesions must be characterized by some special attribute, since inflammation and hyperemia in adult connective tissue are not always followed by the development of carcinomata. In Ribbert's opinion, the process can be best explained on the assumption that those changes which precede the inauguration of carcinoma are the product of certain agents elaborated by the epithelium itself, or, in other words, that the epithelial cells prepare the soil into which they eventually penetrate. But as this chain of events would terminate merely in the growth of normal epithelium, it is necessary to employ the subsidiary assumption that cells which become malignant undergo first a loss in differentiation that enables them to proliferate more luxuriantly. Malignant growths, he believes, can be initiated more readily from embryonal rests than from adult epithelium, because the cells of the former are still in a condition of incomplete differentiation.

In criticism of Cohnheim's hypothesis, it has been asked how it is

[1] *Cohnheim*, Virchows Arch., 1875, lxv, 64.

[2] For a discussion of the relation between heterotopic epithelium and carcinoma, see *Lubarsch*, Verhandl. d. deutsch. path. Gesellsch., 1906, x, 208 (bibl.).

[3] *Ribbert*, Das Karzinom des Menschen, Bonn, 1911, p. 476.

possible for embryonal remnants to develop after having lain dormant for years, but the objection loses its validity when it is recalled that the sexual glands remain quiescent in the body for fourteen or fifteen years, as do the hair follicles of the face in males. Much more damaging is the objection[1] that neoplasms originate wherever the body is exposed to chronic irritation, and that if they develop from embryonal rests these must be distributed throughout the entire body; hence, that this explanation is, in fact, no explanation at all.

As for the hypothesis of Thiersch[2] and Waldeyer,[3] that carcinoma develops in consequence of a disturbance in the restrictions normally imposed by the tissues upon one another, it has been suggested[4] that if tumors were the outcome of a diminution in physiological restraint during later life, they would occur more commonly than they do, and would never arise in young persons.

The view of Hauser[5] and his followers is directly opposed to that of Ribbert. Hauser believes that carcinoma can originate only through a fundamental change in the biological properties of the cells implicated, an assumption which he supports by the occurrence of such changes as loss of physiological function, increase in the size of the cell and its nucleus, the higher chromatin content of the latter, the presence of abnormal mitotic figures, and, finally, the enormous capacity for multiplication. All these characteristics indicate, in his opinion, the appearance of an entirely different type of cell—the emergence of a *new cell race*—the process being, in short, a specific cancerous degeneration. In a transformation like this, a weakening of the defenses said to be erected by connective tissue against epithelium can play but a subordinate rôle. While Ribbert and many other authorities hold that a neoplasm can increase only through the multiplication of its own cells, Hauser and his associates maintain that it spreads by a wave of malignant degeneration which attacks successively the normal structures at its margin.

v. Hansemann,[6] who has exhaustively investigated the types of mitosis found in tumor cells, describes three varieties, distinguished according to their chromatin content as *hypochromatic*, *normal*, and *hyperchromatic*. He explains the increased growth energy of the tumor cell by a gain in the power of independent proliferation and a coincident loss of differentiation; this condition he calls anaplasia. He does not regard it, however, as the prime cause of malignant proliferation, since a growth stimulus is required in addition. When such a stimulus acts upon a normal cell, the outcome is hyperplasia; upon an anaplastic cell, malignant growth. One of the criteria of anaplasia is unequal division of the chromosomes during mitosis, which, followed by an asymmetrical division of the cell, results in the production of elements biologically different from their ancestors. Those mitoses are asymmetrical in which the allotment of

[1] *Bashford*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, pp. ix and 24.
[2] *Thiersch*, Der Epithelialkrebs, namentlich der Haut, Leipzig, 1865, p. 78.
[3] *Waldeyer*, Virchows Arch., 1867, xli, 470; ibid., 1872, lv, 67.
[4] *v. Hansemann*, Die mikroskopische Diagnose der bösartigen Geschwülste, Berlin, 1902, p. 215.
[5] *Hauser*, Das Cylinderepithel-Carcinom des Magens und des Dickdarms, Jena, 1890, p. 135.
[6] *v. Hansemann*, Virchows Arch., 1890, cxix, 299; Studien über die Spezificität, den Altruismus, und die Anaplasie der Zellen, Berlin, 1893.

chromosomes to the daughter stars is unequal; but as the actual number of chromosomes going to each diaster can seldom be accurately enumerated, it is necessary to be content with an approximate estimate. Though v. Hansemann has suggested that irregular mitoses are fairly characteristic of malignant epithelial tumors, they have been found in sarcomata, in benign growths, and even in regenerating normal tissues.[1]

Warburg has suggested that the cause of cancer lies in a selective breeding of cells based on a supposed oxygen deficiency in the tissues. He discovered that the cancer cells can burn glucose anaerobically with the production of lactic acid, while normal cells require oxygen for such combustion and produced only minute quantities of acid. This theory can scarcely be considered as probable. Both the rat placenta, the chick embryo, and the retina have similar capacities and the likelihood is that Warburg has merely demonstrated a special type of metabolism in a group of highly specialized and rapidly growing cells.[2]

None of the various hypotheses has fared so badly at the hands of its critics as that one which would refer neoplasia to the intervention of some parasite. No definite proof has ever been offered in support of this hypothesis, the parasites occasionally associated with tumors (as in the cancer of the rectum and bladder which sometimes accompanies bilharziosis) being regarded merely as the cause of a chronic irritation which, in its turn, gives rise to the new growth. The existence of *cancer villages*, *cancer streets*, and *cancer houses*, together with much of the other evidence so often advanced in support of the parasitic hypothesis, must be viewed with absolute scepticism until more cogent proofs have been brought forward to sustain the contention. It can often be shown, for instance, that a "cancer village" is one in which the population is composed largely of persons in the cancer age, most of the younger ones having migrated to the cities, while those authors who describe "cancer houses" take no account of the law of chance. As has been so well said in discussing this question[3]: ". . . by the law of chance, just as one individual in a thousand may be of gigantic proportions, so one house in a thousand may show a great excess of cases of cancer—or of twin births—over the ordinary run of houses." Furthermore, few of the reports describing the transfer of a neoplasm from one person to another (*cancer à deux*) are in any way convincing. And yet, after all, it cannot be categorically declared that neoplasia is not an infectious process; it can be said only that it does not resemble any of those with which we are at present acquainted.[4]

In regard to diet it is possible to be more definite, and it may be safely maintained that no relation can be discerned between diet and neoplasia, since tumors are discovered with equal frequency in vegetarian races and in those living on a mixed diet; nor is there convincing evidence of a connection between the occurrence of neoplasms and the character of the soil, climate, or other surroundings.

[1] *Podwyssozki*, Zieglers Beitr., 1886, i, 301; *Stroebe*, ibid., 1893, xiv, 154.

[2] *Warburg*, Über den Stoffwechsel der Tumoren, Berlin, 1926; *Warburg*, Jour. Cancer Res., 1925, ix, 148; *Murphy* and *Hawkins*, Jour. Gen. Phys., 1925, viii, 1925.

[3] *Adami*, Principles of Pathology, 2d ed., Philadelphia, 1910, i, 839.

[4] For a vigorous defense of the parasitic hypothesis, see *Emery, W. D.*, Tumours: Their Nature and Causation, London, 1918, and *Gye* and *Barnard*, Lancet, 1925, ii, 109.

In order to gain some insight into the cause of malignant growth, statistics have been collected and analyzed, though without any definite result having been so far achieved. This may, perhaps, be partly because the information has been until within a short time incomplete; thus, the diagnosis has not always been founded upon microscopical examination; the site of the new growth has not been carefully given; the occupation of the patient is not always stated, etc. Statistics are being constantly improved, however, and there is reason to hope that within the next few decades this branch of research may yield valuable information. For example, it cannot be due to chance that workers in aniline dyes frequently have tumors of the bladder,[1] and that those who handle tar develop tumors of the skin.

The chemical investigation of tumors has so far yielded no information of definite value, except that in their composition tumors do not differ widely from the corresponding normal tissue.[2]

The production of a tumor by one single trauma[3] is extremely doubtful. In many cases there can be no question that the association is a coincidence, while in others the injury serves only to direct attention to a tumor already present. Until the cause of malignant growth is definitely understood, however, it will be impossible dogmatically to assert that a single injury cannot give rise to a new growth; but the fact that by far the greater proportion of injuries is not followed by tumor renders the probability infinitesimal. In the case of chronic irritation, the evidence is much more definite. Cancers about the mouth in smokers or in persons with roughened, carious teeth, *x*-ray cancers, and those originating in scars and ulcers spring at once to mind in this connection. That the occurrence of neoplasms in the irritated areas is a matter of pure chance is rendered improbable by the large number of recorded instances, no less than by the observation that the tumors arise exactly at the point subjected to irritation. Occupations and racial habits together constitute, in reality, an extensive experiment.[4] Thus, epithelioma of the skin overlying the abdomen is very common among the natives of Kashmir, who wear a basket of glowing charcoal under their robes for purposes of warmth, and cancer of the mouth is equally common in those natives of India and the Philippine Islands,[5] who chew betel-nut, the neoplasm developing in the former case just where the effects of the heat are most intense, and in the latter at the site where the betel-nut is retained against the cheek. The importance of these observations lies in the fact that cancer in the locations mentioned is practically unknown in other races. Moreover, instances suggesting

[1] *Hamilton, A.*, Jour. Industrial Hygiene, 1921, iii, 16; *Nassauer, M.*, Frankfurter Ztschr. f. Path., 1919–20, xxii, 353.

[2] *Wells*, Chemical Pathology, 3d ed., Philadelphia, 1918, p. 492*ff*.

[3] *Brosch*, Virchows Arch., 1900, clxii, 32; *Schöppler*, Ztschr. f. Krebsforsch., 1911, x, 219; *Schepelmann*, Med. Klin., 1915, xi, 741 (abstr. in Jour. Am. Med. Assn., 1915, lxv, 748); *Wolff*, Die Lehre von der Krebskrankheit, Jena, 1911, Teil ii, p. 125 (bibl.); *Löwenstein*, Beitr. z. klin. Chir. (Bruns), 1906, xlviii, 780; ibid., 1911, lxxiv, 715; Unfall u. Krebskrankheit, Tübingen, 1910; Arch. f. klin. Chir., 1895, xlix, 1; *Graef*, Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1913, xvii, 603; *Stern*, Über traumatische Entstehung innerer Krankheiten, Jena, 1913, p. 487.

[4] *Bashford*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 1.

[5] *Davis*, Jour. Am. Med. Assn., 1915, lxiv, 711.

a relation between chronic irritation and the development of neoplasms are not limited to man alone.[1] In the cow, for example, carcinoma of the liver is almost invariably connected with severe biliary cirrhosis due to infection with a parasite, and is thus complementary to the rectal and vesical cancer which occurs in man in association with infection by the Bilharzia hæmatobia (Schistosoma hæmatobium). The two together show the futility of trying to explain cancer as a disease of civilization. Both organisms, separated as they are in the zoological scale, develop tumors at a point exposed to chronic irritation and apparently in obedience to a law of wide application, since neoplasia assails the entire animal kingdom, at least as far down as the reptiles.[2] It does not attack man because of his civilization, nor does it show any greater preference for cultured than for savage races.[3] It is discovered oftener in highly civilized people because they live to a more advanced age and because they have access to a variety of diagnostic measures denied to the inhabitants of less advanced countries, and not because it occurs more frequently in them. Similarly, cancer does not attack the domestic animals on account of their close association with civilization, sparing wild animals, but develops in the former solely for the reason that they attain higher age periods by reason of man's care, and is discovered in them because they are autopsied with comparative frequency.

The recent successful experimental production of cancer in animals by chronic irritation has shown the importance of this factor in the production of tumors. Carcinoma of the stomach has been produced by feeding white rats with the larva of a nematode worm, which on invading the mucous membrane produces an extensive chronic hypertrophic lesion of the squamous epithelium at the cardia of the organ. After a considerable time has elapsed, a certain proportion of these hyperplasias become malignant and may metastasize.[4]

The repeated painting of the skin of susceptible animals with gas tar over a long period of time, generally a year, has also led to the production of a large number of squamous cell epitheliomata, some of which metastasize into the internal organs, or can be transplanted. Injection of the tar into the breast has produced carcinomata and a very few sarcomata of this organ in animals.[5]

Another interesting example of the effect of irritation by a parasite of an entirely different type is seen in the sarcomata of the liver produced by the infestation of that organ in rats with the cysticercus of Tenia crassicollis, the cat tapeworm.[6] In a susceptible strain of rats as high as 50 per cent. of the animals may ultimately develop sarcoma of the

[1] *Bashford*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 1.

[2] *Murray*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 41. For a résumé of tumors in cold-blooded animals, see *Plehn*, Ztschr. f. Krebsforsch., 1906, iv, 525.

[3] *Bashford*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 1; *v. Hansemann*, Ztschr. f. Krebsforsch., 1914, xiv, 39.

[4] *Fibiger, J.*, Jour. Cancer Research, 1919, iv, 367 (bibl.).

[5] For a complete review of experimental tar cancer see *Woglom, W. H.*, Arch. Path., 1926, ii, 533 and 709.

[6] *Bullock, F. D.*, and *Rohdenburg, G. L.*, Jour. Cancer Res., 1916, i, 87; *Bullock, F. D.*, and *Curtis, M. R.*, Proc. New York Path. Soc., 1920, xx, 149 (bibl.); Jour. Cancer Res., 1925, ix, 425 and 444; and *Borrel*, Bull. de l'Assoc. franc. p. l'Etude du Cancer, 1910, iii, 322.

liver, a tumor never occurring spontaneously in this site in the rat. Within the highly susceptible strain certain families have given a much higher yield of tumors. On the other hand, there are strains in which no tumors, or very few tumors, develop, in spite of the fact that the cysts form in the regular fashion. This crucial experiment demonstrates the importance of tissue susceptibility to an irritant as a factor in the production of a tumor. Such susceptibility has long been suspected as occurring in various human races. The insusceptibility of the skin of the negro to epithelioma, and the great liability of that of the white to the same tumor being a concrete example. In spontaneously appearing tumors, the exact amount of irritation is not however determinable, but in these rat experiments the irritant in both cases is the same, both quantitatively and qualitatively. The ages of the animals, their food, housing and all other conditions are likewise as nearly as possible the same. Therefore the same irritant may produce in one strain a large proportion of tumors and in another a few or none. Thus the liability to cancer is hereditary at least in certain animals, but this is far from the loose general statement so often made that cancer is hereditary.

Chronic irritation, accordingly, appears to be responsible for the inception of certain neoplasms, yet it cannot be the only factor in their etiology, otherwise every person subjected to it would develop a tumor. This, of course, is not the case, and other causes must, therefore, be sought. A second has been discovered by Murray[1] who has found that the offspring of mice suffering from spontaneous (as distinguished from transplanted) carcinoma are about twice as likely to develop such a tumor as are mice descended from normal parents and grandparents.[2] This information must be applied to the human subject, however, only with the greatest reserve since the cancerous ancestry in the mice of these and similar experiments is much more concentrated than ever it would be in human beings. A study of life insurance statistics[3] shows that even among persons whose two parents have died of cancer, the incidence of the disease is no higher than the average. Therefore, while it cannot be denied that there may be found an occasional family with a concentrated cancerous liability, there is, in general, no occasion for alarm.

But the two causes, chronic irritation and predisposition, are in themselves apparently not always sufficient for the inauguration of a neoplasm. A third factor seems to be necessary in most cases, and this is age. By far the largest number of tumors, both in man and in the lower animals, affect individuals who have passed middle life, and in the experiments just cited carcinoma did not develop any earlier in the mice of cancerous ancestry than it did in the other group. Still, in many cases it seems to be not the age of the patient himself that is of importance, but the age

[1] *Murray*, Proc. Roy. Soc., Ser. B., 1911–12, lxxxiv, 42.

[2] See also *Slye*, Jour. Cancer Research, 1916, i, 479, 503; and *Slye, Holmes*, and *Wells*, ibid., 1917, ii, 1, 401; *Tyzzer*, Jour. Med. Research, 1907–08, N. S. xii, 199.

[3] *Hunter*, Address delivered at the Tenth Annual Meeting of the Assn. of Life Insurance Presidents at New York, Dec. 15, 1916.

of the tissue in which the neoplasm originates.[1] This may explain the fact that cancer of the uterus and the gastrointestinal tract appears with relative frequency in middle life, cancer of the skin, on the contrary, rarely before old age.

The Transplantation of Tumors.—While it is possible to transplant living normal tissues or even whole organs into an animal of the same species (*homeotransplantation*) and have them remain viable for a time, their almost invariable fate is sooner or later to undergo necrosis. The results are better when an animal is inoculated with its own tissues (*autotransplantation*).[2] Transplantation into animals of another species (*heterotransplantation*) is not successful.

Turning to the neoplasms,[3] we find that mouse and rat tumors will grow after having been transferred into another animal of the same species, or even into the membrane of chick embryos,[4] and that other information of value is being slowly acquired. Thus, many of the new growths encountered in man are found among the lower animals, though it is to the neoplasms of tame mice and rats that attention has been particularly directed, because of the facility with which these small animals can be stored and handled.

In the mouse, the most common tumor is a carcinoma which originates in the female mammary gland and closely follows the clinical course of cancer in the human subject. Metastasis is common, taking place generally by way of the blood stream, more rarely by the lymphatics, and true infiltrative growth is easily demonstrable. In the rat the neoplasm most often encountered is sarcoma of the connective tissue, or of the liver at the edge of a tapeworm cyst.[5]

It has been found that if small particles of a spontaneous animal tumor be inserted under the skin of healthy young animals of the same species, the implanted cells will grow in a few of them, say about 5 per cent., and within three weeks to several months produce new tumors similar in character to the original. So from animal to animal the tumors may be propagated through long series to an extent which, so far as is now known, is without limit, the percentage of successful inoculations gradually rising in most cases. A striking feature of these transplantations is the apparently boundless capacity of the cancer cell for proliferation, for it will readily be seen that if a few cells can, within a relatively short time, produce a mass as large as the growth from which they came, the amount of new tissue would be prodigious almost beyond belief[6] if all the tumors in every generation were to be transplanted. Yet one should not lose sight of the fact that recent experiments on the cultivation of normal embryonic tissues in vitro suggest that somatic tissues also may be capable of unlimited growth provided that the environment be suitable.

The existence of certain hereditary factors tending to make some mice naturally more, and others less, refractory to *transplanted* cancer has been intimated, and susceptible and non-susceptible strains have been bred.

It has been shown[7] that the cells of a few carcinomata have the power to transform the connective-tissue stroma into a sarcoma, which also is capable of continued propagation, and even tends to overgrow the epithelial portion of the tumor. It is possible that the combination of carcinoma with sarcoma which is occasionally encountered in human neoplasms, may be the outcome of a similar power on the part of the epithelial portions of these growths.

In contrast to the comparative difficulty of getting spontaneous growths to establish themselves in new hosts, is the readiness with which they will succeed in the animals that develop them, for almost without exception they will proliferate if

[1] *Bashford*, Berl. klin. Wchnschr., 1909, xlvi, 1677; Deutsch. med. Wchnschr., 1913, xxix, 4; Middleton Goldsmith Lecture, delivered before the New York Path. Soc., 1912.

[2] *Manley* and *Marine*, Jour. Am. Med. Assn., 1916, lxvii, 260; Jour. Exper. Med., 1917, xxv, 619.

[3] For a résumé of the work which has been accomplished in the field and for bibl., see *Woglom*, Study of Experimental Cancer, New York, 1913.

[4] *Murphy*, Jour. Exper. Med., 1913, xvii, 482; ibid., 1914, xix, 181.

[5] *Bullock* and *Rohdenburg*, Jour. Cancer Research, 1917, ii, 39.

[6] For a calculation of the possibilities of such growth, see *Ehrlich* and *Apolant*, Berl. klin. Wchnschr., 1905, xlii, 871.

[7] *Apolant*, Arb. a. d. könig. Inst. f. exper. Therap., Frankfort a M., Jena, 1906, i, 48; *Haaland*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 175.

reintroduced into the organism in which they are native. This is not because the bearer of a spontaneous neoplasm offers a more favorable soil for tumor growth in general, but because the cells need make no great effort to adjust themselves to their environment, as is necessary for them to do if they are to survive introduction into another animal. The same phenomenon has long been familiar to the surgeon in the form of metastases or of recurrence in the scar or suture holes at the site of extirpation.

Acquired Immunity to Tumors.—This is brought about in an animal by the absorption of cells from another of the same species, and persists for as long as two or three months. Whether the cells be derived from normal tissues or from a tumor, is immaterial; the only requisite is that they shall be living and intact when they are introduced. Thus animals have been rendered refractory to transplantation by the inoculation of embryonic tissues, or adult spleen, kidney, etc., as well as by unsuccessful inoculation with tumors, but it has not been possible to obtain immunity by the injection of juices or extracts from a tumor or by introducing serum from animals possessed of natural or acquired resistance. Experiments in which this outcome has been asserted have been vitiated by lack of care in obtaining such uniform experimental conditions as a pure strain of animals,[1] uniform dosage, etc. Apparently nothing short of the living cell is capable of producing resistance, and the reaction is so delicate that, as has been said, only tissues of the same species are potent. Those of the individual itself, however, are devoid of all immunizing power. The exemption thus conferred, which is due to a failure of fibroblasts and blood-vessels from the host to penetrate the graft,[2] is valid only in the case of a graft which is in the act of establishing itself in a new host, and no substance known will influence a more advanced tumor; nor does immunity prevent the development of a spontaneous new growth. In addition large and unpredictable fluctuations occur even in resistance to implantation and it is impossible to produce it against many highly malignant tumors.[3] Hence there is no justification for the treatment by analogous methods of tumors in man, which, indeed, would be still less likely to yield since they are composed, not of cells foreign to the organism, as is a transplanted mouse tumor, but of native elements.

Classification

It is impossible at present to classify tumors scientifically because our knowledge of their derivation is in many respects incomplete.

None of the schemes proposed is perfect, and they differ from one another in many respects; yet almost all contain the two headings: *connective-tissue* tumors and *epithelial* tumors. If to these there be added a third group, *embryoid* and *mixed* tumors, a classification is obtained which, though admittedly rough, will do for practical purposes. Groups I and II may be subdivided into (*a*) *mature* and (*b*) *immature* growths.

I. (a) Mature Connective-tissue Tumors.—The mature or benign connective-tissue new growths include such tumors as *fibromata, lipomata, angiomata, osteomata,* and *chondromata.* Of them it may be said that their morphological resemblance to the tissue in which they originate is fairly close. Accordingly the two classes of fibrils characteristic of ordinary connective tissue can be recognized in a fibroma by means of Mallory's stain; the adipose tissue of a lipoma closely resembles normal fat; the angioma consists of proliferating blood-vessels; and the cells of osteomata and chondromata prepare bone and cartilage respectively. In no case, however, is the corresponding normal structure exactly duplicated. The fibroma, for example, is apt to be more cellular than connective

[1] It has been observed that mice and rats of different strains, or obtained from different parts of the country, show distinct variations in susceptibility to inoculation with the same tumor.

[2] *Russell,* Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 341.

[3] *Bullock* and *Rohdenburg,* Jour. Cancer Research, 1920, v, 119, 129.

tissue, while in the fat composing a lipoma both cells and lobules somewhat exceed the normal dimensions. The atypical condition of the tissues making up a tumor is demonstrated, again, in the incomplete state of the blood-vessels, most neoplasms being characterized by the scarcity of proper arteries and veins with communicating capillaries, and receiving their blood supply through simple thin-walled channels. The lymph-vessels, too, are abortive, and nerves are said to be ordinarily absent as actual components of the growth.[1]

(b) **Immature Connective-tissue Tumors.**—The malignant connective-tissue group contains the sarcomata. Though the members are composed of unfinished tissue, it is possible to divide them into two classes—one in which the material is totally immature, and a second, in which a certain amount of differentiation has occurred. Those of the former are purely cellular tumors in which the elements produce almost no collagen or other intercellular material characteristic of the site where the growth originates, and appear to expend all their energy in mere proliferation. Such growths, the *round-cell* and *spindle-cell* sarcomata, are among the most malignant of all neoplasms. They have practically no stroma, save for an abundant meshwork of blood-vessels, and as the walls of these channels often consist of a single layer of cells, hemorrhages frequently occur. For this reason, also, tumor cells readily attain the blood-stream, so that the sarcomata metastasize early and extensively by way of the circulation.

The second group is made up of sarcomata showing some effort toward differentiation—toward a production, that is, of an adult tissue like bone or cartilage. Here belong such neoplasms as the *osteoblastic* and *chondroblastic* sarcomata. The attempt is less successful, however, than that which characterizes the benign connective-tissue tumors arising in similar locations and, it is hardly necessary to state, falls still further short of what is seen in the corresponding normal tissue itself.

Differential Diagnosis.—A sarcoma is differentiated from a benign connective-tissue tumor by the scarcity or irregular character of the intercellular material, by variation in the shape and size of the cells, by the presence of an increased number of mitotic figures, and by its invasive growth. From an infectious granuloma it can often be separated by the fact that its elements are all of one variety, whereas infectious lesions contain such dissimilar types as fibroblasts, polymorphonuclear leucocytes, plasma cells, etc. Yet it must be confessed that the distinction between a sarcoma and a benign connective-tissue neoplasm, or between a sarcoma (especially if it be infected) and an infectious granuloma, occasionally proves to be one of the most difficult which the pathologist is called upon to draw.

II. (a) **Mature Epithelial Tumors.**—The benign epithelial series embraces the *papillomata*, *adenomata*, etc., tumors which reproduce more or less faithfully the anatomical features of the structures in which they originate. Thus the adenoma, which develops from glands, imitates the

[1] For a study of nerves in tumors, see *Young*, Jour. Exper. Med., 1897, ii, 1.

parent organ in the arrangement of its epithelium into tubules bounded by a connective-tissue wall, the limits of which its cells have no power to transgress. As the epithelial elements are arranged in one layer about the lumina of these tubules, the resemblance to the normal structure is distinct, though not by any means complete, for there is a larger amount of epithelium than there should be in proportion to the stroma, and this glandular moiety of the tumor is often separated from the excretory ducts of the organ in which the growth is situated.

Tapering glands may appear to have more than one layer of cells, particularly in rather thick sections, because the eye looks down into a funnel of which it sees the sloping sides. This source of error may be eliminated, however, by careful focussing, which will show that the several layers seen are not all in one plane (Fig. 205).

A *B*

FIG. 205.—The sloping sides of a gland in a thick section (*A*) may at first sight create the impression of several layers of epithelium. But careful focussing with high power will show (*B*) that the concentric rows of cells are not all in the same plane.

(b) **Immature Epithelial Tumors.**—The malignant epithelial tumors comprise the various types of *carcinoma*, characterized by the immature condition and arrangement of their epithelium. In these neoplasms, the orderly correlation between epithelium and connective tissue seen under normal conditions and present, though to a smaller extent, in fibroepithelial tumors and the adenomata, is disturbed. The epithelium becomes totally emancipated from all restraint and, breaking through the restrictions normally imposed upon it, attacks and invades the neighboring structures. The more highly differentiated carcinomata mimic the normal pattern to some degree, while at the opposite end of the scale there may be found others in which the epithelium is utterly undifferentiated and arranged in solid masses, making its distinction from sarcoma difficult without the employment of special staining methods.

The connective tissues at the edge of a carcinoma are not infrequently the seat of an infiltration with small round cells, a condition which is regarded by many observers as a defensive reaction on the part of the organism against further advances by the tumor; others (and Ribbert in particular) regard this as a preliminary change in the connective tissue, leading to carcinoma.

III. Embryoid and Mixed Tumors.—The members of Group III are referable to developmental anomalies. *Cystic embryomata* and *embryoid*

tumors of the ovary, testis, mediastinum, and brain, and in the sacral[1] and retroperitoneal regions, appear to originate in unused blastomeres at a very early period in the life history of these elements, the period of cleavage.[2] Hence, these growths contain derivatives of all three germinal layers and approach more nearly than any other to the normal architecture of the adult organism. Elsewhere in the body there occur neoplasms containing products of the three layers and known as *fetal inclusions* or *teratomata,* which may be analogous with the embryomata of the testis and ovary just mentioned.

A subdivision of Group III comprehends the *mixed tumors,* simpler than those of the preceding class, though still very complex in their structure. Under this heading are included mixed neoplasms of the kidney, vagina, bladder, vas deferens, ovary, and testis. These also have their inception in unused blastomeres, differing from the embryoid tumors only in developing at a somewhat later stage in the life history of these elements, that of the three germinal layers.

The malignancy of the mixed tumors varies, but those of the kidney are almost always extraordinarily malignant, and metastasize at an early period.

As a substitute for the term *mixed tumor, complex* or *composite* tumor has been suggested[3] since this more definitely indicates the fact that several tissues take part in the formation of such a growth, and because, furthermore, a true mixture of the various components does not ordinarily occur. Neoplasms made up of two or more modifications of a tissue are not compound, according to this view; a chondrosarcoma is not, for example, since cartilage, bone, and sarcoma are all variants of connective tissue. The constituents must be independent varieties.

By reason of their frequent occurrence, *cystic embryomata* of the ovary deserve a more extended description than can be given to other tumors of this group. Ordinarily from five to ten centimeters in diameter and filled with hair and fatty débris, these are known also as *dermoid cysts,* because their walls are lined with epidermis. From the inner surface of the wall there projects a nodule covered with hair and frequently containing bone in which fully developed teeth may be set. Section of such a mass will usually demonstrate the presence of skin, hair follicles, sebaceous and salivary glands, pharyngeal or nasal mucous membrane, and, more rarely, of thyroid, intestine, or brain. In fact, these cystic embryomata may contain derivatives of any or all the germinal layers, microscopic examination showing their content to be more varied than gross examination would suggest. Solid embryomata are much less often encountered in the ovary than are the tumors just described.

To sum up these complex congenital growths or *teratomata:* They arise by inclusion of portions of another fetus and are thus rather malformations than neoplasms in the limited technical sense. But they may give

[1] For a critical summary of tumors of the sacral region, with bibl., see *Borst,* Centralbl. f. allg. Path., 1898, ix, 449.

[2] For a review of the subject, see *Wilms,* Die Mischgeschwülste, Leipzig, 1897.

[3] *Ribbert,* Geschwulstlehre, 2d ed., Bonn, 1914, p. 638.

rise to tumors, some of them malignant, like chorionepithelioma and sarcoma. Among them are sometimes classed other and simpler congenital anomalies, such as *epidermoid cysts, congenital angiomata,* and the so-called *pigmented nævi* or *moles.*

More than one type of tissue is present in a considerable proportion of all tumors, and it is customary to indicate complexity by compound terms, such as *osteosarcoma, adenocarcinoma,* etc. But some discrimination is necessary in the use of such names, and one should be clear as to what is connoted by these expressions. All new growths have a certain amount of fibrous stroma which carries the blood-vessels and forms a sustaining framework, yet a carcinoma is never referred to as a fibrocarcinoma, no matter how prominent a part the stroma may play in its composition. It is only when a second component assumes an independent growth that it can be justly indicated in the compound name. This may not be easy or always possible to determine, but the desirability of so doing should be held constantly in mind. Unfortunately, compound names are loosely employed by some writers to indicate the seat of a tumor, *osteosarcoma,* for example, being used for sarcoma of a bone, instead of to imply the association of osteoma and sarcoma.

It should also be remembered in this connection that a mixed tumor does not always start as such, but may assume this character by metaplasia (page 78) within the limits of a tissue group. Thus the occurrence of bone or cartilage in a fibroma is common. The possibility of metaplasia should therefore always be taken into account before assuming that a multiplicity of related tissues in a tumor necessarily indicates an embryonal origin.

There are neoplasms which cannot readily be brought into the usual general classification, since they are formed of special kinds of tissue; they have accordingly received distinctive names. Thus there occur peculiar tumors formed of placental tissue called *chorionepithelioma;* of tissue resembling the adrenals, *hypernephroma,* etc.

Cysts.

These structures, for the sake of convenience, are often classed among the tumors, although in general character, structure, and genesis they are usually of an entirely different nature. They may be divided into two classes:

I. CYSTS WHICH DEVELOP FROM PREEXISTING CAVITIES.

1. **Retention Cysts.**—These are chiefly formed by the accumulation of secretion in glands or their secretory ducts, as the result of obstruction to the normal discharge, inflammatory contractions, pressure, etc. The contents are usually mucous, sebaceous, serous, or mixed. To this class belong *comedones, milium, atheroma, chalazion, ranula,* the *ovula Nabothi, milk cysts,* and certain *serous cysts* of the ovaries, Fallopian tubes, gall-ducts, and uriniferous tubules.

2. **Transudation Cysts.**—These arise usually, though not always, as the result of a chronic inflammatory process in lymph-spaces or serous sacs; among them are to be included *ganglion, hydrocele,* etc. Certain *hematoceles* in which blood is extravasated into closed cavities belong to this group.

II. CYSTS WHICH ORIGINATE INDEPENDENTLY AS THE RESULT OF PATHOLOGICAL CHANGES.

1. **Cysts Formed by the Softening and Disintegration of Tissue.**—Such cysts may at first be small, with meager contents and no well-defined wall. A wall may finally develop, either as an entirely new structure, or as the more or less modified capsule of the organ in which they occur. The contents are usually the detritus of the tissue by whose disintegration they are formed. Such cysts are very apt to occur within true tumors, particularly those which are succulent and of rapid growth, since these are very liable to degeneration. Cysts may also appear in the slowly growing tumor-like masses involving the bones in osteitis fibrosa. Finally, old abscesses may be transformed into well-defined cysts.

2. **Cysts Formed around Foreign Bodies.**—The inflammatory reaction induced by the presence of foreign bodies of various kinds, such as parasites, extravasated blood, etc., frequently results in the formation of well-defined encapsulated cysts.

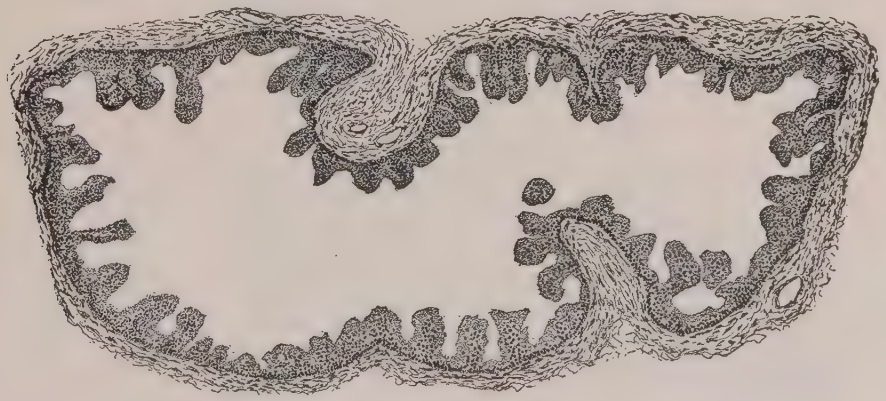


Fig. 206.—Epidermoid Cyst of Skin.

3. **Cysts Formed by a New Growth of Tissues in Whose Spaces Various Kinds of Fluid Accumulate.**—These spaces may or may not be lined with epithelium and have something of the glandular character. Such forms are exemplified in some of the compound ovarian cysts—the so-called *ovarian cystomata,* which are really *adenomata.*

4. **Congenital Cysts.**—These are of various forms, and their mode of origin is in most cases but imperfectly understood. Some of them, like *epidermoid cysts* of the subcutaneous tissue (Fig. 206) and the dermoid cyst of the ovary, are properly grouped among the teratomata. Epi-

dermoid cysts of the skin are probably all formed from an embryonal displacement of the epidermal structures. The simplest forms are lined with epithelium of the squamous type and largely filled with a mass of flat desquamated cells. In the more complicated varieties, hair follicles and sebaceous and sweat glands are present in the lining epidermal membrane. Certain congenital cysts of the kidney and other internal organs are conveniently grouped here, although it is probable that some of them, at least, originate during fetal life in one or the other of the above-described ways, and hence are not essentially different in nature from some of the cysts of other classes. For the mode of formation of certain cysts of the neck see page 746.[1] For cysts of the viscera see Special Pathology.

Various Lesions Sometimes Described as Tumors.

There are certain enlargements of the lymph-nodes which are in reality hyperplasias, sometimes inflammatory in character and sometimes not, and which are often included among the tumors as *lymphomata*. They are not true neoplasms, and will be discussed under lesions of the lymph-nodes. To the same group are often relegated enlargements of the lymph-nodes in leukemia and in other general diseases, which are considered in another part of this book. Another group of tumors sometimes called *lymphomata* are in reality sarcomata.

There is also a class of nodular new formations, the "*infective granulomata*," which in earlier days were placed with the tumors. These, which are now known to be inflammatory, occur in tuberculosis, lupus, leprosy, syphilis, glanders, actinomycosis, etc., and probably include also the nodes of Hodgkin's disease (page 556).

Special Forms of Tumors.

Connective-tissue Tumors—Benign.

FIBROMA.

The fibromata are composed of fibrillar connective tissue[2] which, as under normal conditions, may be dense, collagenous, and firm (*fibroma durum*, Fig. 207), or loose in texture, cellular, edematous, and soft (*fibroma molle*). Since fibrous connective tissue is universally distributed, these tumors may be encountered anywhere in the body. The subdivision into hard and soft forms is not to be taken too seriously, for the dividing line is not distinct and many fibromata contain both hard and soft areas. Fibromata are usually sharply circumscribed and are often encapsulated, though they may be diffuse and merge imperceptibly into the surrounding tissues. They are frequently small and insignificant, but occasionally grow to enormous size. Some

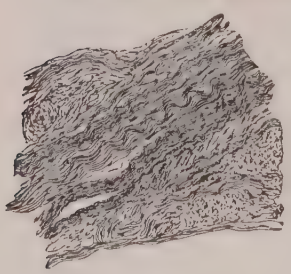


Fig. 207.—Dense Fibroma of Abdominal Wall—Fibroma Durum.

Some of the bands of connective tissue fibers are cut across; others are cut lengthwise.

[1] Consult, for consideration of ciliated and other cysts, *Hess*, Zieglers Beitr. zur. path. Anat., 1890, vii, 98; *Zahn*, Virchows Arch., 1896, cxliii, 170. For later general bibl. of cysts, see *Aschoff*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1895, ii, 456.

[2] For a study of fibroglia, see *Mallory*, Jour. Med. Research, 1904–05, N. S. viii, 113.

fibromata consist almost entirely of intercellular substance containing but few fibroblasts; others contain many.

The younger, growing regions of the tumor are always more or less cellular, but in the older portions, where the cells have had time to mature and produce their characteristic product (*collagen*), the number of elements is small, and those which are present resemble the adult fibroblast in their long slender cell body and their rod-like nucleus. Thus

Fig. 208.—A Nodular Polypoid Tumor—Fibroma—Hanging from the Vulva.

they differ from those in the more cellular parts, which may be of any form, though, on the whole, they appear as plump spindle-shaped elements with oval nuclei. The denser fibromata usually contain but few blood-vessels, although they are occasionally well supplied; many of the softer varieties are very vascular. Both types contain lymph-channels, but like the blood-vessels these are more abundant in the soft fibromata. Nerves are occasionally present—generally preexisting bundles which have been surrounded by the growth.

The course and arrangement of the fibers in these tumors are usually regular. They often cross and interlace in a most complex manner, conferring upon the cut surface an appearance that has been compared to that of watered silk. The fibromata are almost always of slow growth, though exceptionally they increase rapidly in size. They are benign tumors, yet by pressure on important organs, or by ulceration, they may become of serious import. Pure fibromata do not form metastases, but they are often multiple and when so are frequently congenital. They may recur when not fully removed.

Differential Diagnosis.—It is often very difficult, and sometimes even impossible, to distinguish between a rapidly growing fibroma (especially of the soft variety) and a spindle-cell sarcoma. The presence of a great number of cells with large bodies and nuclei, and showing occasional mitotic figures, is suggestive of sarcoma; and the greater their number in proportion to the amount of intercellular substance, the stronger becomes the suspicion of malignancy.

The presence of multinucleated fibroblasts or giant cells sometimes seen in the fibroma molle generally indicates that the tumor is more likely to be a fibrosarcoma than a simple fibroma.[1] These, however, are not often found, and the question must finally resolve itself into which is more abundant—cells or intercellular substance. If the former preponderate, the growth is very like to be a sarcoma, while if the latter be in excess the tumor is probably a fibroma.

It seems probable that in the multiple fibromata of the skin (*fibroma molluscum*) the new growths occur in some special form of connective tissue, as that of the nerves, blood-vessels, or glands. Some of these neoplasms are congenital. There is often a growth of very cellular tissue just beneath the epithelium, and such tumors resemble sarcoma.[2]

The *cheloid* (or *keloid*), composed of very dense fibrous tissue with few cells, often develops rapidly in old skin cicatrices and especially in negroes, forming flat or slightly lobulated tumors. Besides this *cicatricial cheloid*, a *spontaneous* form has been described. But it has been suggested that these do not differ in any way from the cicatricial type, merely following a trivial or forgotten injury, for in predisposed persons even the pressure of a shirt stud or a piercing of the ear lobe may give rise to a cheloid. Strong evidence of the existence of special predisposition is furnished by those cases in which multiple cheloids develop in the scars of acne papules, smallpox pustules, etc.[3] Because of this predisposition, such tumors are not often cured by operation, for another develops in the scar. They can often be removed, however, by compression or by the application of radium or *x*-rays, and sometimes disappear spontaneously. Some authorities deny that the cheloid is a true tumor, preferring to regard it as a tumor-like hyperplasia.

Differential Diagnosis.—The cheloid is distinguished from the fibroma by its typical coarse bands of glassy intercellular substance, and

[1] See, for example, *Kettle*, Pathology of Tumors, New York, 1916, p. 67.
[2] *Gilchrist*, Johns Hopkins Hosp. Rep., 1896, i, 349.
[3] *Lopez-Silvero*, Med. Record, 1917, xcii, 673.

from scar tissue by the possession of large mature cells rich in protoplasm, those of a scar having a small darkly staining nucleus and a cell body of insignificant size.

Fibromata are frequently combined with other forms of tissue to form complex tumors. The looser, softer varieties not infrequently become edematous, closely resembling a myxoma (Fig. 209); other changes which affect the fibromata are calcification and fatty or mucous degenertion, while by metaplasia a fibroma may become a fibrochondroma, fibrolipoma, or fibro-osteoma. The transformation last-named frequently occurs when the tumor develops in the periosteum.

Originating as they do in the connective tissue, fibromata occur in various parts of the body: in the skin and subcutaneous tissue; in inter-

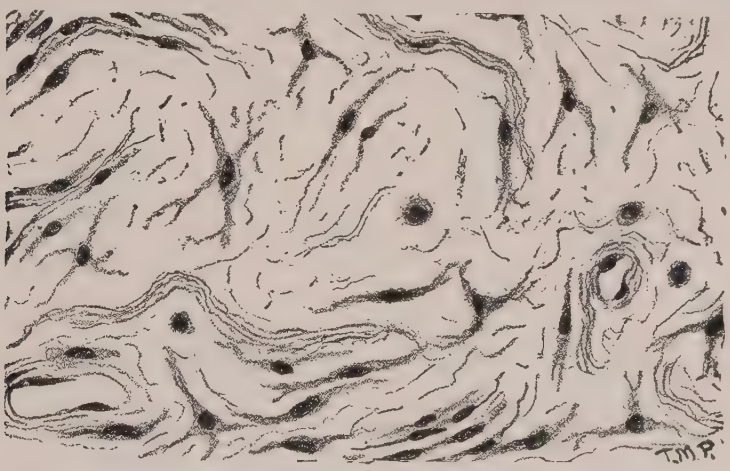


Fig. 209.—Fibroma Molle; from the Subcutaneous Tissue.
The stroma is edematous, and in gross appearance the tumor resembled myxoma.

muscular tissue and fasciæ; in periosteum; in nerve sheaths and intrafascicular connective tissue; in the dura mater; in the interstitial tissue of organs; and in the mucous membranes.

A type of hard encapsulated fibroma occurring in the abdominal wall has received the clinical name of *desmoid.* Polypoid forms occur (Fig. 208).

It is often difficult to distinguish between genuine fibromata and inflammatory or other hyperplasias of the connective tissue such as elephantiasis, and future investigation may perhaps show that the distinctions are not so definite as our classifications suggest.

MYXOMA.[1]

A myxoma is a tumor made up of embryonic connective tissue similar to that of the umbilical cord. The mucous tissue of which they are composed is essentially an embryonic structure, for in the normal adult it is present only in a very imperfect and atypical form in the vitreous of the

[1] *Ribbert,* Frankfurt. Ztschr. f. Path., 1910, iv, 30 (bibl.).

eye, and perhaps occasionally in small amount about the heart and kidneys, and in the medulla of bone.

Myxomata consist in their most typical forms of a homogeneous or finely fibrillated, soft, gelatinous basement substance containing mucin, in which are embedded a variable number of spheroidal, fusiform, branching, and often anastomosing cells (Fig. 210); they may have few or many blood-vessels. By the addition of acetic acid, the mucin may be precipitated from the matrix; in sections the former is usually stained blue with hematoxylin. The very soft forms, which contain comparatively few cells and much translucent intercellular material, are called *myxoma gelatinosum* or *myxoma molle.* The presence of many cells, on the other hand, renders the growth more consistent and confers a whitish and more opaque appearance; such forms are called *myxoma medullare.*

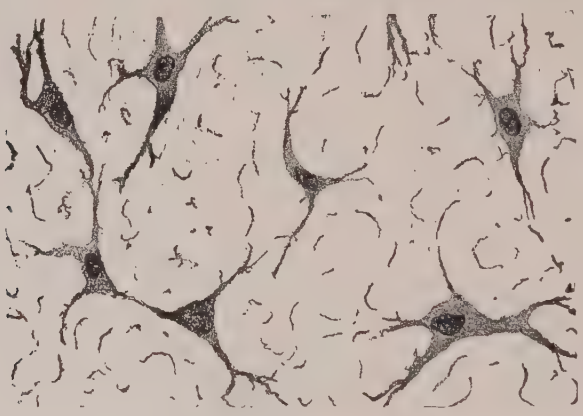


Fig. 210.—Myxoma of Larynx.
Showing the diffuse staining of the mucin-containing stroma with hematoxylin.

The rarity of pure myxomata has led to the assertion that such a growth does not exist; and certainly many of the so-called myxomata have been in truth merely the product of extensive mucoid degeneration in a fibroma, a lipoma, or other variety of connective-tissue neoplasm. Yet there is but little doubt that a true myxoma may occasionally be encountered.

The myxomata may be diffuse, or encapsulated by fibrillar connective tissue; they are frequently very large, sometimes multiple, and often contain cysts and hemorrhages; the cells are likely to undergo fatty degeneration.

Composed as they are of a type of tissue from which fat is developed in the embryo, the relations of the myxomata to adipose tissue are very intimate. Thus they are most frequently developed in, and probably directly from, fat. They are also found, however, in the subcutaneous, submucous, and subserous tissue; in the marrow and periosteum; in the brain and cord; in the sheaths and intrafascicular tissue of peripheral nerves; in intermuscular septa; and in the interstitial tissue of such

glands as the mamma and parotid. Some of the polypi of the mucous membranes are apparently myxomata or fibromyxomata. On the other hand, many of the so-called mucous polyps, those of the nose, for example, are merely edematous hyperplasias of the mucosa, or edematous fibroids;[1] for edematous, loose, and cellular forms of fibrillar connective tissue so closely resemble some of the forms of mucoid tissue that certain observers consider them identical.

The pure myxomata are in general benign; yet they sometimes grow rapidly and occasionally, though rarely, form metastases. In such a case there is an increase in the number of cells and a corresponding diminution in the intercellular substance. Myxosarcoma, often an extremely malignant growth, is distinguished only with the greatest difficulty from a malignant myxoma. Many of these, as has already been intimated in discussing the myxomatous degeneration of benign connective-tissue tumors, are sarcomata which have undergone myxomatous change. Fortunately, however, the distinction is of no practical importance.

LIPOMA.

The lipoma is a common tumor formed of adipose tissue and occurring in the panniculus adiposus or fatty tissues, in the gastrointestinal canal or the peritoneum, or, more rarely, in the dura mater, kidney, liver, and

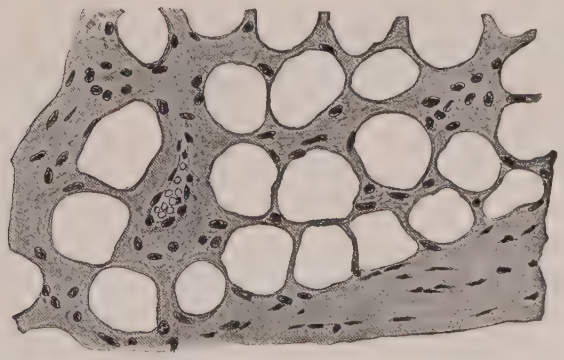


Fig. 211.—Lipoma.
The section shows a small portion of the tumor near the surrounding fibrous tissue.

lung. These neoplasms are usually single, and are sometimes symmetrically arranged in relation to the median dorsoventral plane of the body; as a rule they are sharply circumscribed,[2] and are not infrequently pedunculated. The lipomata are benign growths, though like other benign neoplasms they may do harm by pressure, ulceration, or gangrene, and may recur if incompletely removed. They sometimes attain an enormous size. The adipose tissue of which they are composed (Fig. 211) is arranged in lobules and differs little from normal fat except that

[1] *Wright*, Med. Rec., 1901, lix, 132.

[2] For a review of the literature of *adipositas dolorosa* (*Dercum's disease*), see *Herxheimer* and *Schmidt*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1912, xvi[1], 621.

the cells and lobules are usually larger and less regularly arranged and that the tumor is paler than normal fat, so that even when such a growth is situated in adipose tissue its limits can be readily made out. In congenital lipomata, however, there may be no capsule, and the tumor may be very finely lobulated; this type, therefore, closely resembles normal fat.[1]

Occasionally a considerable number of cells resemble those of embryonic or rapidly growing fat. There may be but little connective tissue in the tumor, in which case it is so soft as to be almost fluctuating (*lipoma molle*), or there may be so much as to give the tumor considerable firmness (*fibrolipoma*); a lipoma may be in part transformed into mucoid tissue (*myxolipoma*), or may become sarcomatous. In some lipomata dilated blood-vessels are a prominent feature (*angiolipoma*). Cartilage formation has been described but calcification and ossification are much more frequent.

CHONDROMA.

These tumors (Fig. 212) are composed of hyalin and fibrocartilage and are usually hard. Fibrous tissue in varying quantity is generally present, either as a perichondrial capsule, or running in bands between the nodules of cartilage, or passing in fascicles into them.[2]

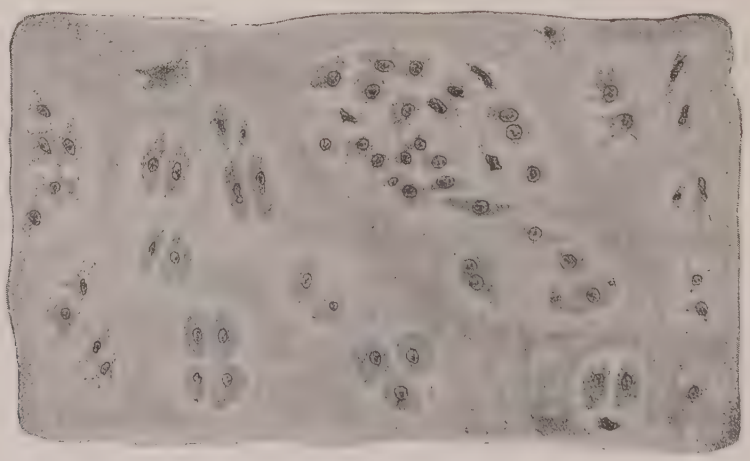


Fig. 212.—Chondroma of Femur.

Like normal cartilage, these neoplasms contain no blood-vessels in their matrix, their nourishment being derived from channels in the bands of connective tissue which surround or penetrate them. This may perhaps explain the lobulated structure which they often assume, no part of the tumor being very far removed from the blood-stream under these conditions.

[1] *Jacobi*, Arch. Pediat., 1884, i, 65; *Brickner*, Am. Jour. Med. Sc., 1918, clv, 473.

[2] For a study of the minute structure of cartilaginous tumors, see *Ernst*, Zieglers Beitr., 1905 xxxviii, 67.

The cartilage may be transformed into mucoid tissue (*myxochondroma*); the cells may undergo fatty degeneration; or the tumor may calcify or ossify (*osteochondroma*). Cartilage frequently forms a part of mixed and complex neoplasms.

Chondromata originate most frequently in connection with bone or cartilage (usually at an epiphyseal line), or in subcutaneous connective tissue or fasciæ. They are not uncommon in the pelvis, where they may interfere seriously with parturition. Chondromata may occur, also, in soft parts where cartilage is not normally present, as in the parotid, testicle, mamma, and ovary; in such cases, however, the cartilage is apt to be mixed with other tissue. Under these conditions, they appear to arise from developmental anomalies. They may develop in the lungs in connection with the bronchial cartilages or from embryonal displacements of portions of these.

The majority of these tumors develop in childhood and early life, whence it has been suggested that they originate from islands of cartilage misplaced in consequence of irregular ossification, such, perhaps, as that which accompanies rachitis. Trauma is said to be an etiological factor, and an hereditary predisposition has long been suspected.[1]

Chondromata are, in general, benign tumors.

The malignant chondromata are softer than others and may even be of gelatinous consistency. While it has been often said that benign chondromata metastasize,[2] critical reexamination of some of the reported instances shows that the phenomenon has occurred in mixed growths containing cartilage rather than in pure chondromata.

Small hyperplastic growths on the surface of cartilages are called *ecchondroses*, and are thus distinguished from the true chondromata, which are known as *enchondromata*.

CHORDOMA.

The chordoma is a rare tumor which originates in remnants of the notochord.[3] In man this is a transient, though important, embryological structure which disappears early in fetal life except for traces remaining in the intervertebral discs (*nucleus pulposus*). The tumor consists of large vacuolated cells with swollen cytoplasm, lying in a homogeneous or finely granulated, jelly-like matrix; these elements readily break down, leaving empty spaces in the intercellular material. The small nodules of notochordal tissue which are an accidental finding in about two per cent. of autopsies, lying at the base of the brain on the clivus just behind the sella turcica, are not regarded to-day as true tumors, but rather as masses of notochordal tissue, possibly hyperplastic, which have been forced out of the bone during fetal development.[4]

Chordomata may occur anywhere along the spinal cord, or develop from the sacrum and coccyx. The small masses at the base of the brain,

[1] *Percy, N. M.*, Surg., Gynec., and Obst., 1915, xx, 619; *Müller*, Zieglers Beitr., 1914, lvii, 232 (bibl.).

[2] For a study of metastases in chondromata, see *Ernst*, Zieglers Beitr., 1900, xxviii, 255.

[3] For a discussion of the embryology of the chorda dorsalis, see *Huber*, Anat. Rec., 1918, xiv, 217 (bibl.).

[4] *Albert, H.*, Surg., Gynec., and Obst., 1915, xxi, 766.

just referred to, are usually benign, but a considerable number of cases is now on record in which such a nodule has developed into a large tumor infiltrating the brain substance,[1] or has grown into the roof of the pharynx.[2] Both benign and malignant growths have been described in the sacrum.[3] In those tumors which reach a large size and show evidence of malignancy, the cells vary considerably from the original type found in the chordal tissue (Fig. 213).

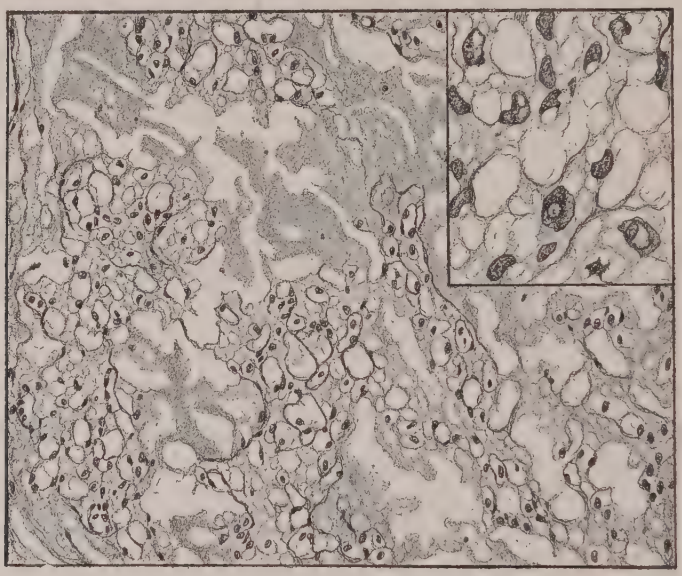


Fig. 213.—Chordoma, Showing the Large Clear Cells, Many of which have Degenerated.

OSTEOMA.

Heterotopia, the presence of tissues at sites where they are not normally found, is well illustrated by bone, which develops under a great variety of conditions and in the most unexpected places. For this reason it is not so easy to define the term osteoma (Fig. 214), and it is often exceedingly difficult to decide whether or not a given mass of bone constitutes a true tumor.

While the true osteoma is rare, bone is often found in tumors of the connective-tissue group as a secondary or complicating structure—*osteofibroma, osteochondroma, osteosarcoma*, etc. It may occur in muscles and fasciæ in consequence of the repeated trauma of athletic exercises (*rider's bone*), or as the result of a peculiar inflammatory process (*myositis*

[1] *Jelliffe* and *Larkin*, Jour. Nerv. and Ment. Dis., 1912, xxxix, 1.
[2] *Linck*, Zieglers Beitr., 1909, xlvi, 573.
[3] *Feldmann*, Zieglers Beitr., 1910, lxviii, 630; *Albert, H.*, Surg., Gynec., and Obst., 1915, xxi, 766. *Wood*, Proc. New York Path. Soc., 1913; *Stewart, M. J.*, Malignant sacrococcygeal chordoma, Jour. Path. and Bacteriol., 1922, xxv, 40 (bibl.).

ossificans), or may appear in connection with chronic inflammations in a variety of tissues—brain, dura and pia mater, pleura, diaphragm, pericardium, skin, choroid, air passages, lungs, kidneys, aorta, penis, and other places. But in order to constitute an osteoma, the bone must show independent growth and must not be of inflammatory origin.

Bony outgrowths projecting from the surface of a bone, and frequently of inflammatory origin, are called *osteophytes* or *exostoses*, similar masses in the substance being known as *enostoses*. These lesions, however, are not true tumors for they do not persist after the exciting cause has been removed; in other words, they do not exhibit independent growth.

Fig. 214.—Osteoma of Humerus.
Eburnated type.

An osteoma may be loose in texture, consisting of spongy bone (*osteoma spongiosum*), or as hard and dense as ivory (*osteoma eburneum*). The difference between these forms lies chiefly in the varying number and size of the vascular and medullary spaces. As a rule, the growth of the osteomata is slow. They are benign tumors, not infrequently multiple, and usually develop in connection with the bone or the periosteum, though they may arise in soft parts.

ODONTOMA.

Each tooth develops from a cap of epithelium fitting over a connective-tissue papilla, the former giving rise to the enamel organ and the latter to the dentine and pulp. From either or both of these, or from the connective tissue surrounding them (*tooth sac* or *follicle*), a tumor may develop (*odontoma, odontoblastoma*); hence, the classification of the odontomata is intricate and not yet entirely settled. Perhaps the best method is that[1] which divides them into those arising from the epithelial cap (*epithelial odontomata*), those springing from cap, papilla, and sac (*composite odontomata*), and those originating from the connective-tissue constituents of the tooth or its follicle (*connective-tissue odontomata*).

The epithelial odontomata, ordinarily known as *adamantinomata*, will be discussed under the benign epithelial tumors (page 458).

Odontomata of all three types are cystic growths which may attain enormous size, though they are, in all probability, always benign. Those of the two latter groups may contain dentine, cement, fibrous tissue, or partially formed teeth.[2]

GLIOMA.

Gliomata (Fig. 215), the most common of the brain tumors, are developed from the characteristic framework of nerve tissue, the neuroglia. Hence, they consist mainly of astrocytes, small cells with round

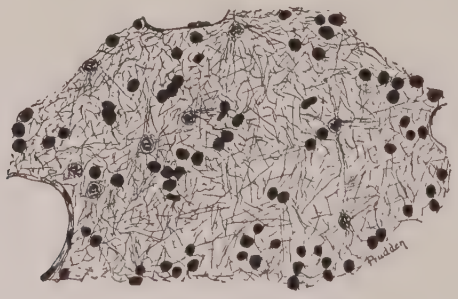


FIG. 215.—GLIOMA OF BRAIN.

or oval nuclei (two or three being occasionally found), inconspicuous bodies, and numerous delicate branching processes. Variations on this type, such as spindle-shaped elements, cells with a large amount of cytoplasm, and polynuclear giant cells, may be present, but the bulk of the growth always consists of astrocytes or "spider cells" (Fig. 216). In order to demonstrate these cells and their branches, it is usually necessary, however, to shake sections of the tumor in water, or carefully to tease small fragments. The nature of the gliar feltwork is not yet entirely clear; for while it was held by Weigert that it is composed of fibrils lying

[1] *Gabell, James,* and *Payne,* see editorial article in Brit. Med. Jour., 1915, ii, 103. For a discussion of the various classifications, see *Bonney* and *Ellis,* Surg., Gynec., and Obst., 1917, xxiv, 459; *Kaempfer,* ibid., 1911, xii, 357; *Malassez* and *Galippe,* Les débris épithéliaux paradentaires, Paris, 1910, p. 233.

[2] A discussion of the odontomata of man and the lower animals may be found in *Bland-Sutton's* Tumors, Innocent and Malignant, New York, 1917, p. 211.

close beside the cytoplasm, rather than of actual cell processes, more modern authorities[1] believe that much of it represents branches of the astrocytes. But the occurrence of some independent fibrils is not denied.

In certain gliomata the elements are to be found in *rosettes*, or alveoli, produced by arrangement of the cells about lumina. These structures imitate the ependyma, the side of the cell toward the lumen being free and the other ending in prolongations into the surrounding tissues. These, more than any other of the gliomata, most clearly reveal their ectodermal origin. The cells constituting these rosettes are identical with the spongioblasts, according to Ribbert,[2] who calls the tumor composed of such elements *spongioblastoma*. He regards this growth as genetically identical with the pure glioma, which is merely a more fully differentiated spongioblastoma. In their typical form, consisting, that is, of well-developed astrocytes, gliomata are found only in the brain and spinal

Fig. 216.—Neuroglia or Spider Cells from Glioma of Brain. Teased specimen.

cord and at the roots of the cranial nerves. These tumors often contain thin-walled dilated blood-vessels, and since they are liable to interstitial hemorrhage may be mistaken at autopsy for apoplectic clots. They may be soft or moderately hard and, especially when growing in the substance of the brain, are not, as a rule, sharply outlined against the adjacent normal tissue; this is because, in spite of the fact that they are benign tumors, they grow by invading the surrounding brain. Cysts and large areas of necrosis are often found and the tumors may undergo fatty degeneration. Gliomata usually occur singly and are comparatively slow in growth. They metastasize in the brain and cord, but not in distant organs, perhaps because their cells are too highly specialized.[3]

Technically speaking, pure gliomata are benign tumors, but their situation in the brain makes them almost always dangerous, for as much as an entire hemisphere may be compromised; furthermore, beside ultimately destroying life by increasing the intracranial pressure or by

[1] *e.g.*, *Stroebe*, Zieglers Beitr., 1895, xviii, 405.
[2] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 456.
[3] For a very complete study see *Bailey* and *Cushing*, Classification of the Tumors of the Glioma Group, Philadelphia, 1926.

invading some vital portion of the brain, they may cause paralysis or sudden death from intracerebral hemorrhage. On the other hand, even a large tumor may cause but few symptoms.

All gliomata do not consist of the relatively mature astrocytes which characterize these neoplasms in the brain. Thus, gliomata of the retina consist largely of a less differentiated element—a small round cell with but a minimal amount of cytoplasm and practically no branches. Mingled with these, however, there may be found both mature glia and epithelial rosettes resembling those found in gliomata of the brain and cord. Thus, as Ribbert[1] points out, the cells of a retinal glioma, which are descended from neuroblasts of the early retinal anlage, produce epithelium, gliar cells, and an indifferent element.

Retinal glioma is an extremely malignant neoplasm, which has occurred in nearly all the cases during the first four years of life. Unless the eye be promptly enucleated, the tumor grows forward into it, destroying the sight, or backward into the brain, the other eye being often involved secondarily via the optic nerve. The tendency toward its development appears to be hereditary.[2]

Gliomata have been described, also, in connection with the sympathetic nervous system,[3] occurring almost without exception in the medulla of the adrenal. These growths are made up of small cells with deeply staining nuclei, embedded in a fine feltwork, and showing a tendency to collect about masses of the fibrillar ground substance in the form of "rosettes." A number of authorities[4] insist that such neoplasms are not gliomata, but *neuroblastomata* (page 419).

NEUROCYTOMA.

There arise in the nervous system other neoplasms besides the glioma, which, as has just been said, originates from the supporting substance. These others, involving embryonal antecedents of the nervous system, or more fully developed functional elements such as the ganglion cell, have been carefully investigated during the past few years, but they are comparatively rare growths and many questions regarding them are still open. Since the benign and malignant tumors in this group are not clearly separated from one another, it will perhaps be most advantageous to discuss both classes here.

The following diagram[5] reproduces current conceptions regarding the development of the sympathetic system, in which most of these growths originate, and will make clear the relationship of these neoplasms to one another.

Neural ectoderm (neurocyte) → Primary sympathetic cell (sympathogonion) { Sympathoblast → Sympathetic ganglion cell. / Phäochromoblast → Chromaffin cell.

[1] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 470.
[2] *Griffith*, Brit. Med. Jour., 1917, i, 850; see also *Hansell*, Am. Jour. Dis. Child., 1915, ix, 485.
[3] *Schilder*, Frankfurt. Ztschr. f. Path., 1909, iii, 317.
[4] *e.g.*, *Wiesel*, Virchows Arch., 1905, clxxx, 553.
[5] Modified from *Landau*, Frankfurter Ztschr. f. Path., 1912, xi, 26.

Those embryonal cells which are destined finally to produce the entire nervous system are called by Kohn[1] and others *neurocytes*, and by Held[2] *neurogliocytes*. The sympathetic portion of the nervous system originates from a special group of neurocytes belonging to the embryonal spinal nerves (Kohn). Sympathetic neurocytes emerge relatively late from their surroundings in the form of deeply staining elements with vesicular nuclei, gathered into groups which anastomose with other groups by means of cell processes; often, however, these cells fuse to form a multinucleated protoplasmic mass or syncytium. At a somewhat later period of intrauterine life they appear as small round cells between which fine nerve fibrils can be discerned.

One tumor composed of neurocytes—a *neurocytoma*—has been described.[3] This growth, discovered in the Gasserian ganglion of a man fifty-six years old, consisted of groups of entirely undifferentiated, round, oval, or polygonal cells with a homogeneous protoplasm and a vesicular nucleus. No fibrils were present, and the elements composing the growth thus resembled the neurocyte in its earliest, least differentiated state.

Even by the time that the embryonal sympathetic neurocyte has reached its next stage, the *primary sympathetic cell*, or *sympathogonion*, it has progressed but little toward the form which it is finally to assume as a member of the nervous system. The sympathogonion appears, accordingly, as a neutral or indifferent element, no more characteristic in its structure than the lymphocyte; in other words, it is merely a small round cell with a deeply staining nucleus, and exhibits none of the features associated with fully developed nervous tissue save some slight fibrillar differentiation.

The sympathogonion gives rise to two series of cells—(*a*) the *sympathoblast*, characterized by a nucleus larger and more vesicular than that of the sympathogonion, and by a proportionately wider cytoplasmic rim; and (*b*) the *phäochromoblast*, which goes through similar changes, but develops in addition an affinity for chrome salts.

NEUROBLASTOMA.

The second (sympathogonion) stage in the development of the sympathetic system is represented by the *neuroblastoma*,[4] a malignant neoplasm that may involve any part of the nervous system, though it is far more common in the sympathetic, and usually in the adrenal[5] or elsewhere behind the peritoneum, whence it metastasizes most frequently to the liver, the skeletal system, and the lymph-nodes. The cases so far reported have occurred almost without exception in infants or children, and the younger is the child the more immature histologically, and malignant clinically, is the growth apt to be (cf. *ganglioneuroma*).[6] The

[1] *Kohn*, Arch. f. mikros. Anat., 1907, lxx, 266.
[2] *Held*, Die Entwicklung des Nervengewebes bei den Wirbeltieren, Leipzig, 1909.
[3] *Marchand*, Festschrift. f. Rindfleisch, 1907.
[4] For a review of the literature, see *Lehman*, Jour. Med. Research, 1917, N. S. xxxi, 309; *Lambert, R. A.*, Proc. New York Path. Soc., 1917, xvii, 96.
[5] *Herxheimer*, Zieglers Beitr., 1914, lvii, 112 (bibl.).
[6] *Freifeld*, Zieglers Beitr., 1915, lx, 347 (bibl.).

fact that there are only some twenty-five instances in the literature should not be interpreted to mean that this neoplasm is extraordinarily rare. It is not; for there is a large number of doubtful cases on record,

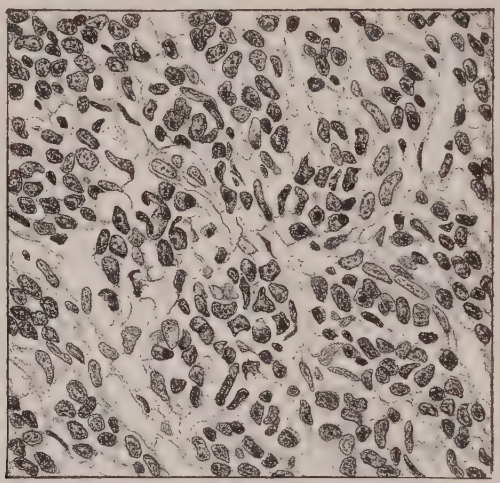


FIG. 217.—NEUROBLASTOMA OF KIDNEY.

FIG. 218.—NEUROBLASTOMA.
Showing rosettes, one of which is drawn under higher magnification in the upper right-hand corner of the plate.

some of which were in all probability true neuroblastomata, and to these must be added all early unrecognized examples described as sarcoma of the adrenal.

The neuroblastoma (Fig. 217) is composed largely of sympathogonia (*sympathetic neuroblasts*), which show a tendency to gather in solid masses or in hollow spheres inclosing a mass of fibrils; these latter are the "rosettes" (Fig. 218), which, however, do not morphologically resemble similarly named structures in the glioma. The tumor contains, also, fine fibrils, often arranged in bundles, which are probably embryonic nerve fibers, and hemorrhagic and necrotic areas.

Differential Diagnosis.—The diagnosis is not easy, and until the last few years these tumors have been passed over as sarcomata. The following features, among others, have been advanced as characteristic:[1] Location in the adrenal or elsewhere in the retroperitoneal region of a young child; the presence of cells with small round nuclei rich in chromatin and surrounded by an extremely narrow rim of cytoplasm which tends to flow out into processes; the tendency of these elements to collect in groups, or to gather in rings about masses of fibrillæ ("rosettes"); and finally, the occurrence of a fibrillar matrix staining neither as collagen nor as gliar fibers.

SYMPATHOBLASTOMA.

The next stage of the developing sympathetic nerve cell is represented by the *sympathoblastoma*, a malignant new growth occupying a place midway between the immature neuroblastoma and the mature ganglioneuroma, and composed of sympathoblasts. One such neoplasm has been discovered,[2] in the cervical sympathetic of a two and a half year old boy. It was made up chiefly of cells not so small as the sympathogonion and containing a large (8 to 12 micra) oval nucleus.

GANGLIONEUROMA.

The ganglioneuroma[3] consists mainly of ganglion cells, the most mature elements of the series now under discussion. However, it should be borne in mind that not only do tumors of the sympathetic division merge almost imperceptibly into one another, but that cells in all stages of development may occur in the same neoplasm. Thus, Wahl's neuroblastoma contained a whole scale of elements, running from the entirely undifferentiated neurocyte at one end, to the fully differentiated ganglion (Fig. 219) or chromaffin cell at the other, imitating in miniature, therefore, the complete normal development of the sympathetic neurocyte.[4] Similarly, the ganglioneuroma contains elements reminiscent of phases earlier than the ganglion cell, although the greater part of the growth resembles fully developed nervous tissue more completely than the neurocytoma, the sympathoblastoma, or even the neuroblastoma.

Like most other neoplasms, the ganglioneuroma reflects the comparative maturity of its cells in clinical benignancy, only those immature portions which are occasionally present and which correspond to the

[1] *Wahl*, Jour. Med. Research, 1914, N. S. xxv, 205; *Landau*, Frankfurt. Ztschr. f. Path., 1912, xi, 26.
[2] *Martius*, Frankfurt. Ztschr. f. Path., 1913, xii, 442.
[3] *Peters*, Frankfurt. Ztschr. f. Path., 1913, xiii, 114 (bibl.); *Freund*, ibid., 266.
[4] See also *Robertson*, Virchows Arch., 1915, ccxx, 147.

neuroblastoma, being malignant. As with the neuroblastoma, the younger is the patient bearing a ganglioneuroma, the more undifferentiated and malignant is the growth apt to prove.[1]

The ganglioneuroma may occur at any age, but more commonly affects children and young adults, and is rather rare after forty. It may arise anywhere in the nervous system, though most of them have involved the sympathetic; here they appear most often in the abdominal portion,[2] frequently in the adrenal. This growth is not quite so rare as the neuroblastoma, about fifty cases having been recorded.

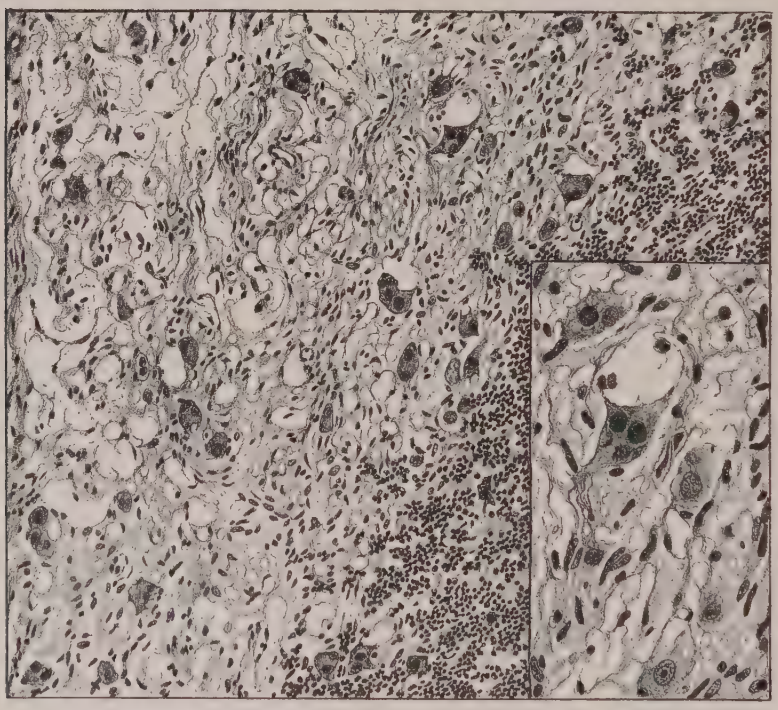


Fig. 219.—Neuroblastoma Containing Ganglion Cells.

Ganglioneuromata, being comparatively mature, contain nerve fibers (usually non-medullated) and ganglion cells—large round, oval, pyramidal, or polygonal elements with one or more nuclei. The fibers often preponderate over the cellular constituents. But since the whole tumor is not always completely differentiated, there may be found an admixture of entirely immature small round cells resembling the lymphocyte (sympathogonia), or of somewhat more mature elements with large vesicular nuclei (sympathoblasts). Gliar portions, also, derived from peripheral glia, are not an uncommon finding (*ganglioglioneuroma*).

[1] *Falk*, Zieglers Beitr., 1907, xl, 601.
[2] *Dunn*, Jour. Path. and Bacteriol., 1914–15, xix, 456.

PARAGANGLIOMA.

(Phäochromoblastoma or Chromaffin Tumor.)

The rare tumor composed of chromaffin cells is known as a paraganglioma.[1] The neoplasms of this group are benign growths found in the parasympathetic (chromaffin) system, particularly in the medulla of the adrenal and in the carotid gland (Fig. 334 and 335).

Of those involving the adrenal only about a dozen cases have been described, though it must be remembered that their nature has been recognized only within the last decade and, accordingly, they may not be so uncommon as this statement seems to imply. They are usually small and are discovered, as a rule, in middle-aged and elderly persons, being found sometimes accidentally at autopsy; they are not infrequently associated with *neurofibromatosis*. In such cases they may perhaps be viewed as but one manifestation of a general disturbance of the entire nervous system. Since the cells of the adrenal paragangliomata resemble in appearance the fully developed chromaffin cell, or, in other words, are comparatively mature, these growths correspond to the ganglioneuromata. No tumor occupying an intermediate developmental stage, made up solely of phäochromoblasts, and analogous, therefore, with the sympathoblastoma, has yet been discovered.

Like most other growths of the sympathetic division, the adrenal paraganglioma contains cells in various stages of differentiation. The preponderating elements are large epithelium-like cells, in which adrenalin and glycogen can often be demonstrated; these frequently assume a characteristic brown stain after fixation in chrome salts, although the reaction is not invariably demonstrable, possibly because those cells in which it is absent are not yet fully differentiated, being still in the phäochromoblast stage. The characteristic mature chromaffin cell appears as a polymorphous or polyhedral element with a finely granular vacuolated protoplasm, while sympathogonia, transitional forms, multinucleated giant cells, ganglion cells, and cystic or hemorrhagic areas may be encountered; medullated or non-medullated nerve fibers are occasionally found.[2]

The paraganglioma of the carotid[3] is about as rare as that of the adrenal, but as it has been recognized for a longer time, more cases have been recorded; thus, about sixty have been described in the past twenty-five years or so. It is usually a slow-growing, benign neoplasm, although metastasis or recurrence has been described in some cases (25 to 30 per cent.), and reproduces in the main the structure of the carotid gland. It consists, therefore, of alveoli separated by capillaries and containing cuboidal, round, or oval nuclei and a comparatively abundant cytoplasm which may be granular or vacuolated. These cells sometimes show very

[1] For a review of the literature, see *Wahl*, Jour. Med. Research, 1914, N. S. xxv, 205, and *Harbitz*, Arch. Int. Med., 1915, xvi, 312.

[2] *Herxheimer*, Zieglers Beitr., 1914, lvii, 112.

[3] *Paltauf*, Zieglers Beitr., 1892, xi, 260; *Mönckeberg*, ibid., 1905, xxxviii, 1; *Keen* and *Funke*, Jour. Am. Med. Assn., 1906, xlvii, 469; *Callison* and *Mackenty*, Ann. Surg., 1913, lviii, 740; *Balfour* and *Wildner*, Surg., Gynec., and Obst., 1914, xviii, 203; *Wetterdal*, Hygiea, 1916, lxxviii, 1761 (abstr. in Jour. Am. Med. Assn., 1917, lxviii, 401); *Gronemann*, Virchows Arch., 1914, ccxviii, 163 (bibl.).

definitely their chromaffin nature by assuming a yellowish hue after fixation in solutions of chrome salts. Giant cells and syncytial masses are occasionally found.

NEUROFIBROMATOSIS.

Neurofibromatosis (*von Recklinghausen's disease, fibromata nervorum*)[1] is a disorder characterized by the appearance of multiple tumors of subcutaneous and other nerves; by areas of pigmentation varying in hue from light to dark brown; and, less often, by a condition resembling elephantiasis (*elephantiasis neuromatosa*); in some of the cases mental abnormalities or stigmata of degeneration have been present. The most constant change, however, is the presence in the subcutaneous tissues and skin

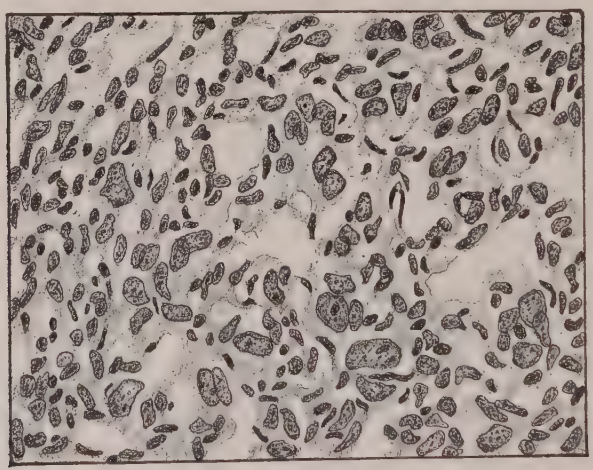


Fig. 220.—Neurofibrosarcoma of Musculospiral Nerve.

of hundreds or even thousands of new growths varying from the size of a pinhead to that of an orange. Trauma, even so slight as the pressure of the clothing, is said to be followed by the appearance of fresh nodules. The tumors are generally soft, freely movable, and not tender. The diffuse involvement of an entire plexus produces the *plexiform neuroma*, while a mass of nodules resembling a bunch of grapes, forming a more isolated mass with a single pedicle, and without intimate connection with a nerve trunk or a plexus, is called a *racemose neuroma*.[2]

An hereditary predisposition often underlies von Recklinghausen's disease, which, indeed, may even be congenital. Sarcoma (Fig. 220) sometimes develops after the removal of the deep-seated tumors, though more frequently following the extirpation of a plexiform neuroma. When all forms are considered, this change has been discovered in 12.5 per cent. of the cases (Harbitz). Furthermore, the coexistence of von

[1] *Preiser, S. A.*, and *Davenport, C. B.*, Am. Jour. Med. Sc., 1918, clvi, 507 (large bibl.).
[2] *Harbitz*, Arch. Int. Med., 1909, iii, 32.

Recklinghausen's disease with other neoplasms (glioma, paraganglioma, and even carcinoma and sarcoma) is not rare.

Microscopical examination of the lesions of neurofibromatosis shows that all the tumors arise from the connective tissue of the nerves (the endo- and perineurium), and that they are accordingly simple fibromata (Fig. 221) through or around which the nerve fibers pass. While the most generally received opinion is that these growths originate in the sheath of Schwann, a few observers[1] believe that the lesions are not

FIG. 221.—NEUROFIBROMA.

fibromata, but a product of the proliferation of Schwann's cells or analogous elements; since these are regarded as peripheral glia cells, the neurofibroma would then be comparable to the glioma. For this reason, the term *neurinoma* (= nerve fiber tumor) has been proposed as describing the condition more accurately.[2]

A condition possibly related to von Recklinghausen's disease, is that in which one or more neurofibromata similar to those described in the preceding paragraph are found in the nerves, without the existence of

[1] *e.g.*, *Verocay*, Zieglers Beitr., 1910, xlviii, 1.
[2] *Verocay*, Zieglers Beitr., 1910, xlviii, 1.

cutaneous tumors or pigmentation; they involve localized regions such as the spinal nerve roots, the arm, the optic and auditory[1] nerves, etc.

The *painful subcutaneous tubercle* (*tuberculum dolorosum*) is a single, small, hard, subcutaneous fibroma or neurofibroma which is sometimes exquisitely sensitive. It is more common in women than in men.

NEUROMA.

The term neuroma was attached indiscriminately to all tumors of the nerves until Virchow separated the *false neuroma* (composed largely of connective tissue) (Fig. 222, 223, and 224) from the *true* (consisting chiefly of nervous material). The latter he subdivided into three types: *neuroma gangliocellulare*, containing newly formed nerve cells; *neuroma*

FIG. 222.—FALSE NEUROMA—FIBROMA OF LUMBAR NERVE.
The fibrous tissue is loose in texture and in places edematous, so that many of the nerve fibers pass through the tumor with little structural alteration.

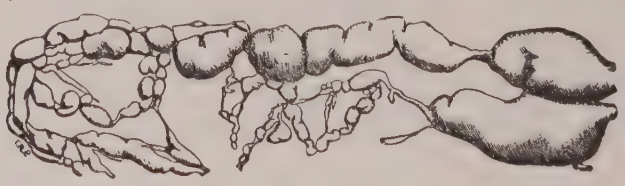


FIG. 223.—MULTIPLE FIBROMATA (FALSE NEUROMATA) OF PNEUMOGASTRIC NERVE.
From the same case as that from which the photographic reproduction of Fig. 224 is made. One-quarter natural size.

fibrillare amyelinicum, made up of non-medullated nerve fibers; and *neuroma fibrillare myelinicum*, composed of medullated nerves. His fibrillar neuroma, however, does not satisfy those who regard nerve fibers as processes of the ganglion cell and who, therefore, deny that a pure nerve tumor can exist, since the axon is unable to proliferate independently. This school, which constitutes the majority, will admit to a place among the true neuromata only such growths as contain ganglion cells. The

[1] *Cushing*, Tumors of the Nervus Acusticus, Philadelphia, 1917.

FIG. 224.—MULTIPLE FIBROMATA (FALSE NEUROMATA) OF THE PERIPHERAL NERVES OF THE ARM AND LEG.

A, Nerves of the right arm; *B*, the left sciatic with its branches; *C*, the left anterior crural with its branches. From the same case as Fig. 223. The nerves of the other extremities were similarly involved.

opposite and newer school, on the contrary, regards the elements of the sheath of Schwann as genetically equivalent to the ganglion cell, and asserts that the occurrence of neuromata comprised solely of nerve fibers can be readily explained, since it is from the sheath of Schwann, and not from the nerve cell, that the axon develops.[1]

According to the older school of *centralists*, von Recklinghausen's disease would be an example of multiple false neuromata; but Durante,[2] an adherent of the newer *peripheralist* view, holds that all growths of the nerves are true neuromata and that in proportion as the newly formed nerve tissue persists in an immature stage or differentiates out to form myelin, the tumor will be *amyelinate* or *myelinate*. von Recklinghausen's disease would therefore be a true *polyneuromatosis*, in which the nerve tissue assumes a fibrous appearance instead of differentiating into young fibers or persisting in a myelinogenous stage as do the cells of other neuromata. *Myxomata* of the nerves would also be true neuromata that have undergone myxomatous transformation.

Pending the settlement of these questions, the true neuromata may be conveniently divided into the *ganglioneuroma*, which has already been described, and the *fibrillar neuroma*. Of Virchow's two subdivisions of this latter type, the myelinic variety is the more common and the better understood, though both are extremely rare tumors. It is a benign growth consisting of medullated nerve fibers,[3] intricately curved and intertwined, as a general rule, and associated with some fibrous tissue. Centralists[4] explain the absence of ganglion cells by assuming atrophy of those formerly present, or[5] by referring the fibers to ganglion cells situated outside the growth. On the other hand, it has been suggested[6] that many of the neoplasms described as neurofibromata, under the influence of von Recklinghausen's work, may actually have been true neuromata; the opposite, however, is more likely to be true—that most of the neuromata reported before the appearance of his monograph were really fibromata. At any rate, it is significant that since the publication of von Recklinghausen's paper, the bibliography contains many descriptions of fibromata of the nerves, but almost none of true fibrillar neuromata.[7] Finally, it is possible that transitions may occur between von Recklinghausen's disease and the true neuromata.[8]

While the diagnosis of myelinic neuroma can easily be confirmed by Weigert's myelin stain, that is, of course, not applicable in the case of the amyelinic variety, the identification of which is often extraordinarily difficult, since the tumor so closely resembles a fibroma. The non-medullated neuroma is a grayish neoplasm usually involving the sympathetic nervous system. Its fibrils are colored somewhat less intensely

[1] For an account of this controversy, which is not by any means settled, see *Bruce* and *Dawson*, Rev. Neurol. and Psychiat., 1913, xi, 117.

[2] *Durante*, Rev. neurol., 1906, xiv, 836; article, Nerfs, in Cornil and Ranvier's Manuel d' histol. pathologique, iii, Paris, 1907 (abstr. in Centralbl. f. allg. Path, 1908, xix, 21).

[3] *Barile*, Lo Sperimentale, 1910, lxiv, 269 (abstr. in Centralbl. f. Path., 1911, xxii, 410).

[4] *Beneke*, Zieglers Beitr., 1901, xxx, 1.

[5] *Adami*, Principles of Pathology, 2d ed., Philadelphia, 1910, i, 752.

[6] *Knauss*, Virchows Arch., 1898, cliii, 29.

[7] *Borst*, Die Lehre von den Geschwülsten, Wiesbaden, 1902, i, 234.

[8] *Aschoff*, Ergebn, d. allg. Path., 1898, v, 90.

with eosin than those of connective tissue, showing on cross section as small discs; cut in a longitudinal direction they appear in bundles and hence may be mistaken for smooth muscle.[1] It is said that the axis-cylinders in these growths can rarely be stained by those special methods which are employed to demonstrate them in normal tissue. This, however, may be because most of the neoplasms regarded as amyelinic neuromata have really been fibromata, and the attempt should always be made in doubtful cases.

To sum up the fibrillar neuromata, it is the consensus of opinion[2] that such growths do not exist independently of the ganglion cell, and that all growths described as fibrillar neuromata are really ganglioneuromata in which the ganglion cells either have disappeared or else occupy a position outside the growth. The so-called *amputation neuroma*, a tangled mass of nerve fibers sometimes found in the stumps of amputated limbs, is relegated by most authorities to the regenerative processes, no longer occupying a position therefore among the true neoplasms.

MYOMA.

A myoma is a neoplasm composed of either non-striated or striated muscle.

Leiomyoma: Myoma levicellulare.—The parenchyma of this tumor consists of non-striated muscle cells—overlapping fusiform elements with long rod-like nuclei. They lie closely packed into bands which

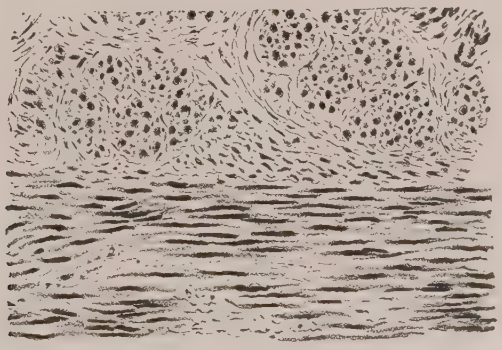


FIG. 225.—MYOMA OF UTERUS.
This is of the smooth-muscle type—leiomyoma—and shows one bundle of muscle cells cut lengthwise, others across.

run in various directions and are separated from adjacent bands by a variable quantity of more or less vascular fibrous connective tissue (Fig. 225). The pure leiomyoma, in which the amount of stroma is minimal, occurs principally in the female genital tract, the urinary tract, the gastrointestinal canal, the skin,[3] and sometimes in the veins.[4]

A much more common type is the *fibromyoma*, a leiomyoma contain-

[1] *Henke*, Mikroskop. Geschwulstdiagnostik, Jena, 1916, p. 89.
[2] *Pick* and *Bielschowsky*, Ztschr. für die gesamte Neurol. u. Psychiat., 1911, vi, 391.
[3] *Lieber*, Zieglers Beitr., 1915, lx, 449 (bibl.).
[4] *Schnyder*, Centralbl. f. Path., 1914, xxv, 529.

ing a large amount of connective tissue; it should be remembered, however, that no matter how great the quantity of this material, muscle is still the primary constituent of the growth (Fig. 226). This we believe because the younger is the neoplasm the smaller is the proportion of connective tissue, very recent growths being made up almost entirely of muscle. Since these tumors, then, are myomata, the term *myofibroma* should not be applied to them, though it often is.

The muscle cells in a myoma, as well as their nuclei, vary considerably in shape; both may be long and slender or short and plump, the latter form prevailing especially in more rapidly growing tumors, wherein

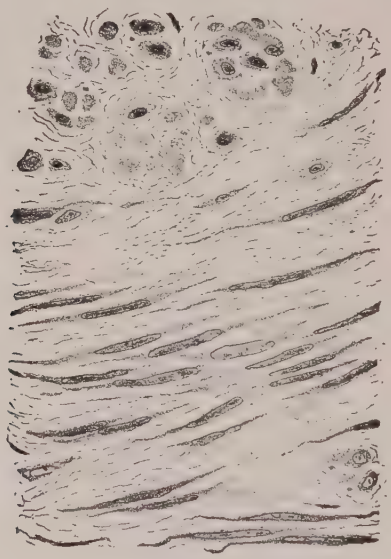


FIG. 226.—FIBROMA OF UTERUS.
The muscle cells are crowded apart by dense fibroma tissue.

mitotic figures may perhaps be discovered as additional evidence of rapid proliferation. Myoglia fibrils are demonstrable, frequently presenting considerable variation in size and arrangement.[1]

Fibromyomata may occur wherever smooth muscle tissue exists, but are most commonly found in the uterus, where they are often called *fibroids*, from their resemblance to the fibroma; here they are not uncommonly multiple. They have been found also in the wall of the gastrointestinal canal and in the kidney, bladder, and skin, while a certain proportion of the hypertrophies of the prostate are sometimes regarded as leiomyomata of the interstitial muscle of that gland.

As a rule, they grow slowly and are benign, but, especially in the uterus, they may be large enough to lead to serious disturbance or even to threaten life, without being malignant. In this situation, too, they may become edematous by reason of some disturbance in their circulation and, owing to their poor blood supply, not infrequently

[1] For methods of staining these fibrils, see *Mallory*, Jour. Med. Research, 1904–05, N. S. viii, 113.

degenerate, forming cysts or undergoing gangrene; hyaline degeneration and calcification are not rare.

While leiomyomata are usually benign, as has already been said, a few instances are on record in which rapidly growing invasive and metastasizing neoplasms of this type have been found in the uterus,[1] gastrointestinal canal,[2] bladder,[3] etc. In such a growth (*malignant leiomyoma*, *myosarcoma*, or *myoma sarcomatodes*) the nuclei of many of the muscle cells are round, oval, or irregular, and, like the cell bodies, variable in size; mononuclear and polynuclear giant cells have been described (see Fig. 611, page 960). On the other hand, the connective-tissue portion of a fibromyoma may become sarcomatous.[4]

Differential Diagnosis.—It is not always easy to distinguish a leiomyoma from a spindle-cell sarcoma or a cellular fibroma, or in a fibromyoma to decide what is muscle and what connective tissue. The following general rules, however, may be suggested: The muscle cell is sharply outlined and has a long rod-shaped nucleus with rounded ends, which lies within the cell body; that of the fibroblast, on the contrary, is spindle-shaped, relatively shorter, and lies on the surface. Muscle does not show so definitely the wavy striations characteristic of connective tissue and is apt to contain more nuclei in a given field. Again, the muscle cell usually terminates in a definite pointed extremity, while the tip of the fibroblast is apt to break up into an arborization of fine fibrils; these characteristics are best studied in fresh preparations which have been treated with 35 to 50 per cent. sodium or potassium hydroxide solution to dissociate the cells from one another. Finally, the tinctorial properties of the cells are sometimes of assistance; thus muscle is more strongly acidophile than connective tissue and therefore takes a more intense red color in sections stained with eosin; where doubt still exists Van Gieson's stain (muscle, yellow; connective tissue, red) or Mallory's (muscle, red; connective tissue, blue),[5] may be employed.

For a description of adenomyoma of the uterus, see page 957.

Rhabdomyoma: Myoma striocellulare.—In this extremely rare tumor, striated muscle fibers are the characteristic elements. These, however, very rarely compose the greater part of the growth, but are intermingled with other elements, such as fibrillar connective tissue, and spheroidal or spindle-shaped cells which often appear to be incompletely developed muscle cells. The fibers differ, as a rule, from those of normal striated muscle in their arrangement, which is generally quite irregular, and in their size and appearance, being in general smaller than normal fibers, although they vary greatly; droplets of glycogen can frequently be demonstrated, and the sarcolemma is usually absent or incompletely developed. These neoplasms, which do not ordinarily attain a large size, are supposed to develop from misplaced embryonal muscle cells.

Rhabdomyomata arising in muscle are said to be *homologous*. About

[1] *Hoevels*, Frankfurt. Ztschr. f. Path., 1911, viii, 477.
[2] *Eising*, Jour. Path. and Bacteriol., 1903, viii, 233; *Ghon* and *Hintz*, Zieglers Beitr., 1909, xlv, 89.
[3] *Lexer*, Deutsch. med. Wchnschr., 1904, xxx, 42; *Roder*, ibid., 485.
[4] *Ricker*, Virchows Arch., 1895, cxlii, 211.
[5] *Mallory*, Jour. Med. Research, 1904–05, N. S. viii, 113.

twenty cases[1] have been recorded in the heart, all in children and often associated with multiple congenital cerebral sclerosis; but this type is a malformation rather than a true tumor.[2] *Heterologous* rhabdomyomata originate at sites where striated muscle is not normally found, the great majority being confined to the genitourinary organs, where they generally form part of a mixed tumor;[3] an exceptional case of rhabdomyoma occurring in the parotid gland, however, has been recorded by Prudden.[4] These growths, when not associated with other and malignant tumors, are usually benign and are of greater theoretical than practical interest. Only a few malignant rhabdomyomata have been reported in man;[5] one has been described in the trout.[6]

ANGIOMA.

Angiomata are neoplasms consisting largely or entirely of blood- or lymph-vessels or cavities. It often happens that newly formed or old blood- or lymph-channels become prominent in a tumor by reason of

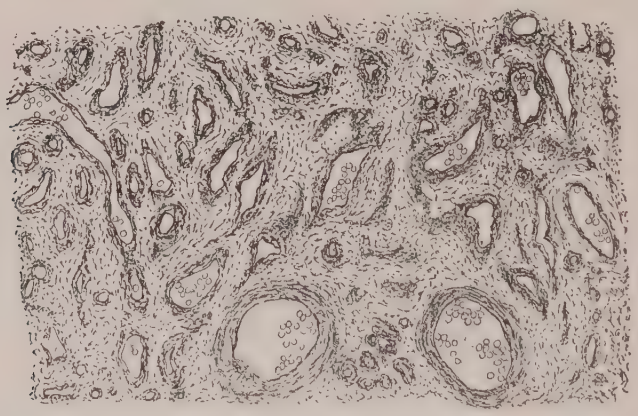


FIG. 227.—ANGIOMA TELANGIECTOIDES FROM SKIN.
This section is from a vascular nævus, strawberry mark, of the skin.

their dilatation or their great number, and those of otherwise normal tissues may be of increased caliber as in arterial varices, cirsoid aneurysms, hemorrhoids, and various lymphectasiæ; none of these, however, is a true angioma, because the vessels do not proliferate independently.

Angiomata are of two kinds: I. *Hemangioma*; II. *Lymphangioma*.

[1] The earlier literature has been reviewed by *Wolbach*, Jour. Med. Research, 1907, N. S. xi, 495. Later articles are those of *Abricossoff*, Zieglers Beitr., 1909, xlv, 376 (bibl.); *Bundschuh*, ibid., 1912, liv, 278; *Rehder*, Virchows Arch., 1914, ccvii, 174; *Ribbert*, Centralbl. f. allg. Path., 1915, xxvi, 241; and *Kawamura*, Centralbl. f. allg. Path., 1913; xxiv, 801 (bibl.).

[2] *Fujinami*, Virchows Arch., 1900, clx, 203; *Stumpf*, Zieglers Beitr., 1911, l, 171.

[3] *Wilms*, Die Mischgeschwülste, Leipzig, 1902; *Spuler*, Centralbl. f. allg. Path., 1905, xvi, 337; *Squier, J. B.*, Rhabdomyoma of prostate, Surg., Gynec., and Obst., 1916, xxiii, 341.

[4] *Prudden*, Am. Jour. Med. Sc., 1883, lxxxv, 438.

[5] *Stoerk*, Ztschr. f. Heilk., 1901, xxii, 200: *Burgess*, Jour. Med. Research, 1913–14, N. S. xxiv, 447; *Muller*, Jour. Cancer Research, 1917, ii, 393 (bibl.).

[6] *Adami*, Montreal Med. Jour., 1908, xxxvii, 163.

I. Hemangioma.[1]—Of this there are three types: 1. That variety (Fig. 227) formed largely of capillary blood-vessels embedded in a more or less abundant connective-tissue stroma, and known as *capillary angioma, angioma simplex,* or *angioma telangiectoides;* its channels are frequently dilated or pouched and usually form an intricate mass of curled and intertwined vessels. Such growths occur most frequently in the skin or subcutaneous tissues, usually about the face, and may be either level with the surface (*vascular nævus, strawberry mark,* or *port-wine stain*) or raised above it (*blue wart*). They are ordinarily congenital and either circumscribed or diffuse. Besides the face, they involve the mucous membranes, mamma, brain, and bones, and, in fact, any part of the body except the cornea and the cartilages (Kornmann, *l.c.*). In themselves these angiomata are benign tumors as a rule, almost never forming metastases,[2] but they may be associated with sarcoma. Except in so far as an angioma is a deformity it is of but little clinical significance, save for the rather rare variety found in the pelvis of the kidney, which may give rise to fatal hemorrhage.[3]

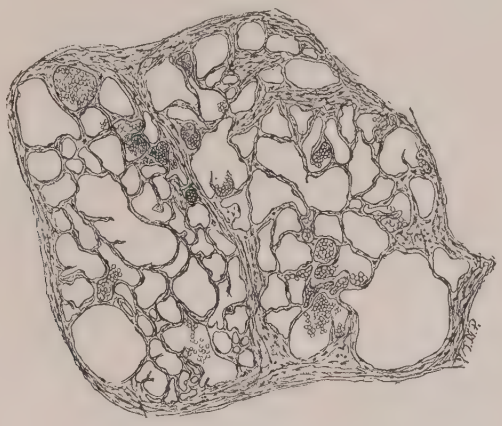


FIG. 228.—ANGIOMA CAVERNOSUM OF LIVER.
This section shows the entire small tumor.

2. The second form of hemangioma (*angioma cavernosum*) consists largely of a series of intercommunicating blood-spaces, irregular in shape and size (Fig. 228), lined with endothelium, and surrounded by a variable quantity of fibrillar connective tissue which may contain smooth muscle cells. It resembles the erectile tissue of the corpora cavernosa and the clitoris and is apparently produced by a dilatation of old and newly formed capillaries and veins. It is sometimes erectile or pulsating and not infrequently multiple. Tumors of this sort may be seated in the skin and subcutaneous tissue, where they form the *nævus prominens,* or in the

[1] For a review of the literature, see *Kornmann,* Hämangiome, Odessa, 1913; abst. in Centralbl. f. allg. Path., 1914, xxv, 526.

[2] See, however, *Borrmann,* Zieglers Beitr., 1907, xl, 372; *Shennan,* Jour. Path. and Bacteriol., 1914–15, xix, 139.

[3] *Kettle,* Pathology of Tumors, New York, 1916, p. 124.

internal organs. They are found often in the liver,[1] less frequently in the bones, brain, spleen, uterus, kidney, intestine, bladder, and muscles. They are usually of little significance, though they may give rise to hemorrhage.

To a place among the true tumors neither the capillary nor the cavernous angioma is admitted by some authors,[2] who believe that these growths possess no power of independent proliferation and include them, therefore, among the malformations; thus, E. Albrecht[3] regarded the cavernoma of the liver as a *hamartoma*, or developmental error. Others, on the contrary,[4] assert that they do grow, and sometimes even invasively.

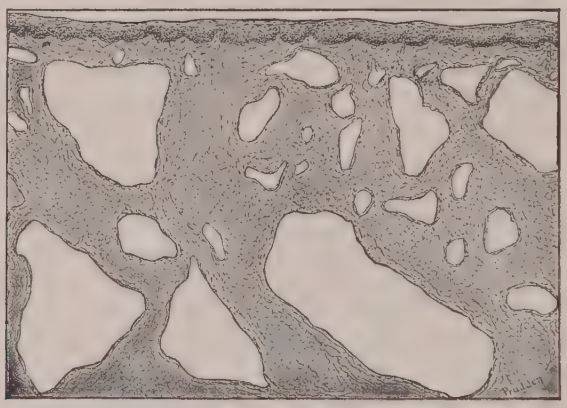


Fig. 229.—Congenital Lymphangioma from Arm of Child.

3. Only a third class is acknowledged by the former group as a genuine neoplasm. In this variety, to which the term *angioma simplex hypertrophicum* was applied by Ziegler,[5] the capillaries show unmistakable evidences of proliferation in their prominent cubical endothelial cells, of which there may be several layers. Since it is the endothelium that grows so vigorously, tumors of this group may be, and often are, considered endotheliomata.

II. Lymphangioma.[6]—All that has been said regarding the doubtful right of the hemangiomata to a place among the true tumors, applies to the lymphangiomata. These consist of dilated lymph-vessels which usually preserve approximately the general shape of the original channels, though they may be distinctly cavernous in character (*lymphangioma cavernosum*, Fig. 229), or even cystic (*lymphangioma cysticum*). The

[1] *Roggenbau*, Zieglers Beitr., 1910, xlix, 313.

[2] *e.g.*, *Adami*, Principles of Pathology, 2d ed., Philadelphia, 1910, i., 814. For a discussion of the controversy, see *Fischer* and *Zieler*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1904–5, x, 815.

[3] *Albrecht, E.*, Verhandl. deutsch. path. Gesellsch., 1904, vii, 153; Frankfurt. Ztschr. f. Path., 1907, i, 221.

[4] *e.g.*, *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 200.

[5] *Ziegler*, Lehrbuch d. allg. Pathologie, Jena, 1905, i, 423.

[6] For bibl., see *Fischer* and *Zieler*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1904–5, x, 842; *Herxheimer* and *Schmidt*, ibid., xvii, 636.

vessels are generally filled with a translucent or milky fluid resembling normal lymph and are separated by more or less connective tissue.

Lymphangiomata are most often congenital, but are sometimes acquired. The simple lymphangioma usually occurs in the skin as a soft swelling, the cavernous type in the tongue (*macroglossia*) or in the lip (*macrocheilia*), and the cystic in the neck (*cystic hygroma*).[1] All are benign tumors, which, however, may rupture and give rise to serious lymphorrhea.

An infrequent tumor, best classified under the angiomata, is one which occurs in the subcutaneous tissues, frequently subungual. These glomic tumors are made up of endothelial cells, blood vessels, nerve ele-

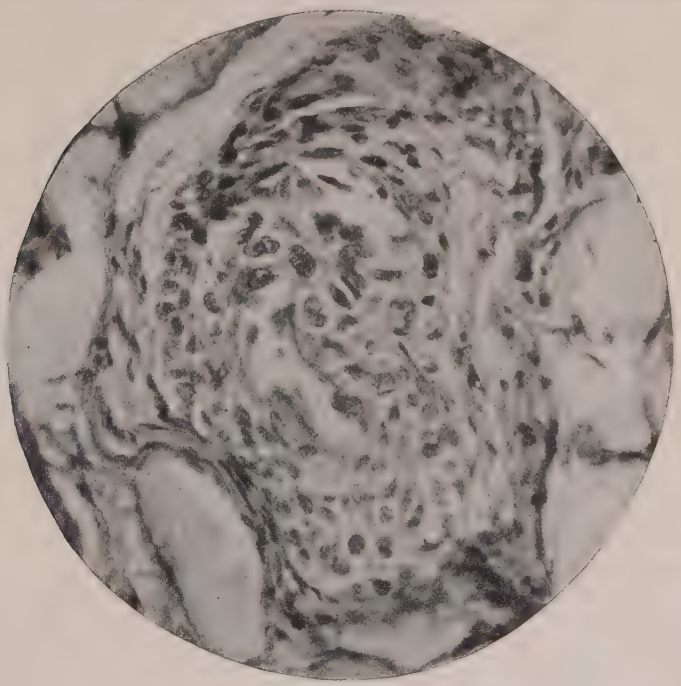


FIG. 230.—GLOMIC TUMOR FROM FINGER TIP. × 375.

ments, and occasionally a few striated muscle fibers (Fig. 230). Their chief interest is that they are intensely painful, resembling in this regard the painful subcutaneous nodules mentioned on page 426.[2]

XANTHOMA.

(*Xanthelasma.*)

This is included for convenience among the neoplasms, though by many authorities it is regarded simply as a connective-tissue reaction following the collection of cholesterin esters (page 56) in the cells of the

[1] For a discussion of the surgical aspects of this condition, see *Winslow*, Surg., Gynec., and Obst., 1917, xxv, 428.

[2] *Prodanoff*, Ann. d'anat. path., 1927, iv, 147; *Masson* and *Gery*, ibid., 1927, iv, 153.

affected site. It is usually a small, flat, yellowish prominence, situated most often in the skin about the eye (*xanthoma palpebrarum*), sometimes elsewhere on the body surface, and occasionally in an internal organ; there may be more than one lesion, and cases of *xanthomatosis* (*xanthoma multiplex*) have been described.[1] Either type may be hereditary.

Under the microscope the xanthoma (Fig. 231) is found to be composed of large foamy cells, with one or more darkly staining nuclei; in

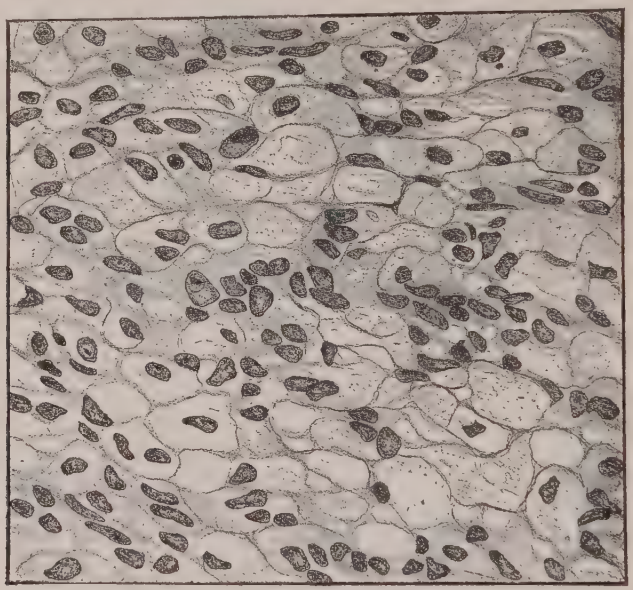


Fig. 231.—Xanthoma of Elbow.
Showing large foam cells.

preparations that have not come into contact with alcohol it can be demonstrated that the spaces in the protoplasm are due to the presence of fat, fatty acids and cholesterin esters. As a rule the cell contents do not stain very deeply with dyes of the Sudan type, taking only a reddish tinge. With polarized light it is usually possible to make out finely doubly refractile granules. Some of the tendon sheath tumors often contain considerable areas of xanthoma cells. The chief interest in the xanthomata is in differential diagnosis. They have occasionally been mistaken for giant cell sarcomata or for metastatic hypernephromata. That they are not tumors but merely related to the degenerative processes is shown by the fact that if the patient is so treated that the amount of blood cholesterin is diminished, a certain number of xanthomata disappear. Xanthoma appears most often in patients with diabetes or jaundice,[2] conditions which are associated with cholesterinemia.

[1] *Sikemeier*, Frankfurt, Ztschr. f. Path., 1913, xiv, 428; *McFarland* and *McConnell*, Jour. Med. Research, 1904, N. S. vii, 69.

[2] *Pinkus* and *Pick*, Deutsch. med. Wchnschr., 1908, xxxiv, 1426; *Schulte*, Zieglers Beitr., 1916, lxi, 570 (bibl.); *Major*, J. Hop. Hosp. Bull., 1924, xxxv, 27.

Connective-tissue Tumors—Malignant.

SARCOMA.

Unlike the benign connective-tissue tumors, the sarcoma often produces but an insignificant quantity of the intercellular material[1] characteristic of the tissue whence it originates or, at the most, elaborates a diminished amount of an imperfect product in comparison with the normal standard. It tends, therefore, to be composed predominantly of cells, whereas the normal connective tissue consists largely of a matrix containing only enough cells to prepare and maintain it; between these two extremes, however, lie not only the benign connective-tissue tumors, of which both cells and intercellular material are prominent constituents (see page 408), but a group of sarcomata (*fibrosarcoma*, *osteosarcoma*, etc.) in which the matrix is nearly as abundant as it is in the benign growths of the connective tissues.

The connective tissue of a sarcoma sometimes forms a network of large meshes dividing the growth into alveoli (*alveolar sarcoma*). Whatever its disposition, however, the cells always stand in intimate relationship with it, as is revealed by the fact that fine fibrils can be demonstrated between the individual elements or even in continuity with them. Blood-vessels, also, form a constant and important structural element in the sarcomata, being in some of them so conspicuous as to give structural outline and general character to the neoplasm. Like those of normal connective tissue, they are intimately associated with the basement substance, but unlike these are rudimentary, their walls consisting often of a single layer of endothelium, even when the vessel is of comparatively large size.

The cells of a sarcoma resemble in appearance such actively growing connective-tissue elements as are found in the developing embryo or in granulation tissue. In outline they vary from a spheroidal shape to that of a spindle or a cylinder, and may be large or small.

Sarcomata are most frequently found in the skin, subcutaneous and subserous connective tissue, fasciæ, marrow, periosteum, and choroid. They involve also, though more rarely, the dura mater, brain and cord, lymph-nodes, adventitia of blood-vessels, nerve sheaths, submucous tissue, uterus, ovary, and kidney. In the liver, pancreas, lungs, and heart, they may appear, but usually by metastasis.

Though sarcomata do occur in early life they are not more common at this time than in later years, as they are ordinarily said to be; on the contrary, they develop more frequently in the higher age periods,[2] as the carcinomata do (see page 463).

The cellular character of most sarcomata, their rapid growth, vascularity, and tendency to recurrence and metastasis, stamp them on the whole as malignant tumors. But in this respect they vary greatly, for

[1] For a discussion of this question, see *Hulisch*, Zieglers Beitr., 1915, lx, 245 (bibl.).

[2] *Weinberg* and *Gastpar*, Ztschr. f. Krebsforsch., 1904, ii, 216, 220; 1906, iv, 18; *Bashford* and *Murray*, Second Sci. Report, Imperial Cancer Research Fund, London, 1905, i, 24; *Roger Williams*, Natural History of Cancer, New York, 1908, p. 322; *Weller*, Arch. Int. Med., 1915, xv, 518; Jour. Michigan Med. Soc., 1915, xiv, 524; *Harbitz* and *Platou*, Norsk. Mag. f. Lægevidensk., 1917, lxxxviii, 145 (abstr. in Jour. Am. Med. Assn., 1917, lxviii, 1074).

while some varieties belong in every sense to the most malignant of all neoplasms, others grow slowly, are very dense, and may remain localized and harmless for years. Their tendency in this respect will be mentioned under the special forms.

Intimately related as they are to the blood-vessels, metastasis is more apt to occur by way of the circulation than through the lymph-channels, and adjacent lymph-nodes are consequently much less apt to be involved than by some other types of neoplasm, notably the carcinomata. Richly cellular and vascular sarcomata are especially prone to hemorrhage, degeneration, and ulceration.

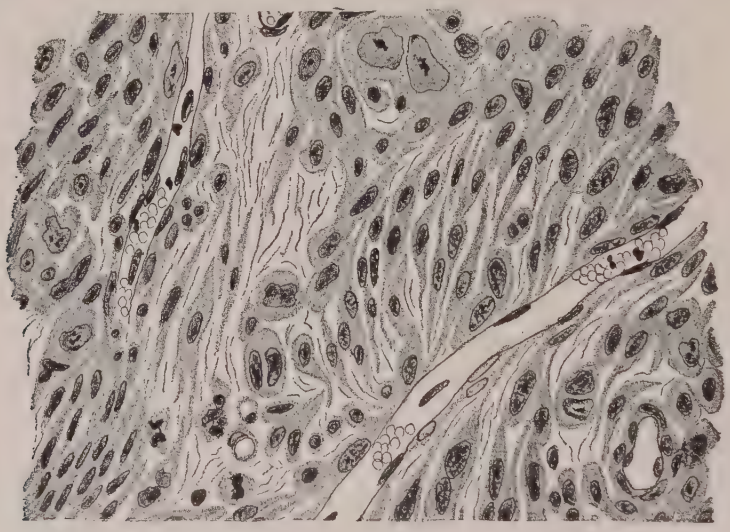


Fig. 232.—Large Spindle-cell Sarcoma.

A single variety of element is often so conspicuous as to furnish a suitable qualifying name for the tumor, though in many cases the cell form varies widely in the same growth (*polymorphous-cell sarcoma*). It may be said, in the main, that some tendency is shown by the sarcomata to reproduce the special characteristics of the tissues in which they originate; thus those of the bones may be *osteosarcomata*, those of fibrous connective tissue *fibrosarcomata*, and so on. It will be more convenient for our present purpose to describe briefly the most common forms one after another than to attempt any systematic classification of them; it should be remembered, however, that the various types are not sharply defined, but are apt to merge into one another and to intermingle in various ways.

Spindle-cell Sarcoma.—The cells of these tumors may be large (*large spindle-cell sarcoma*, Fig. 232 and 233) or small (*small spindle-cell sarcoma*, Fig. 234). The growth may consist almost entirely of cells or, on the other hand, contain so much intercellular fibrous tissue that it may appropriately be called a fibrosarcoma; but different parts of the same

neoplasm often differ greatly as to the proportion between cells and intercellular material. The cells are frequently arranged in fascicles which surround the blood-vessels and cross and interlace in an intricate pattern. Accordingly, almost any section from a spindle-cell sarcoma will contain some elements which have been cut at right angles to their long diameter, or obliquely, appearing therefore to have a circular or an oval outline.

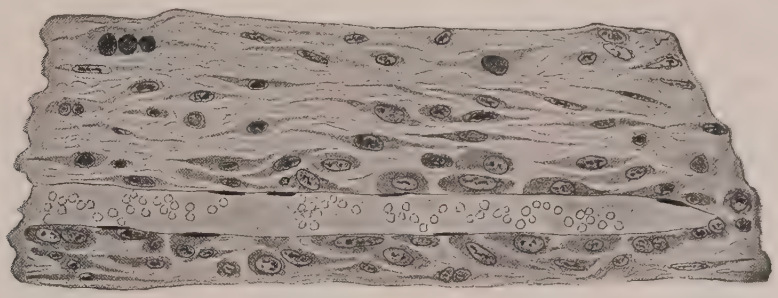


FIG. 233.—LARGE SPINDLE-CELL SARCOMA.
Showing abundant cell growth near a blood-vessel.

Care should be taken not to make the diagnosis of polymorphous-cell sarcoma in such cases.

The spindle-cell sarcomata, especially the small cell variety, are, as a rule, denser, firmer, and less malignant than other kinds, though to this statement there are many exceptions; they may be encapsulated or infiltrating. To this class belong those growths formerly described as *fibroplastic tumors* and *recurrent fibroids*. The spindle-cell sarcoma most frequently arises in the periosteum, subcutaneous tissue, and muscles,

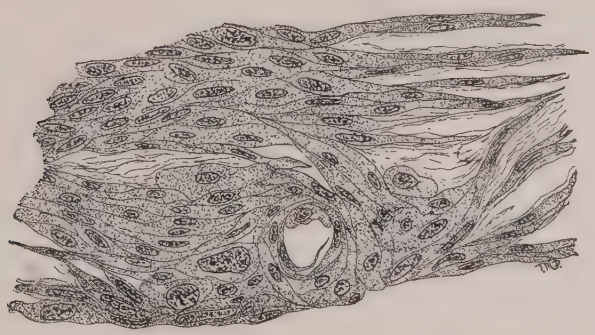


FIG. 234.—SMALL SPINDLE-CELL SARCOMA OF FOREARM.

but it is seen also in the uterus and in various glands, notably the mamma, testis, thyroid, etc. It is among the most frequent of the sarcomata.

DIFFERENTIAL DIAGNOSIS.—See Fibroma, page 408.

Round-cell Sarcoma.—Of this there are two classes: 1, *small round-cell sarcoma*, and, 2, *large round-cell sarcoma*.

1. The small round-cell sarcoma consists of elements similar in size

and appearance to the lymphocytes of the lymph-nodes (Fig. 235) and of a variable amount of intercellular substance which, as in the spindle-cell variety, may be either irregularly distributed or arranged in a network. So small is the quantity of intercellular material in many cases, however, that it is difficult of detection without special modes of preparation. Tumors of this class sometimes contain many blood-vessels, and may be soft and succulent. Their growth is frequently rapid and they are often extremely malignant; they are apt to metastasize widely and early, perhaps because their cells are so small as to be easily transportable from one site to another They occur most commonly in the connective tissue of the muscles and fasciæ, in the skeletal system, and in the internal organs.

2. The cells of a large round-cell sarcoma (Fig. 236) vary in size, but are usually much larger than those of the small-cell variety. Their

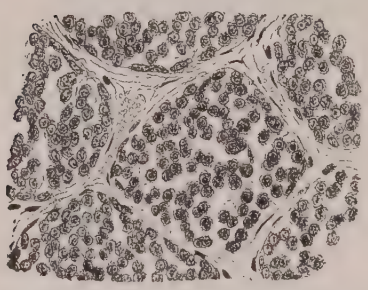


Fig. 235.—Small Round-cell Sarcoma. From a metastatic tumor in the lungs.

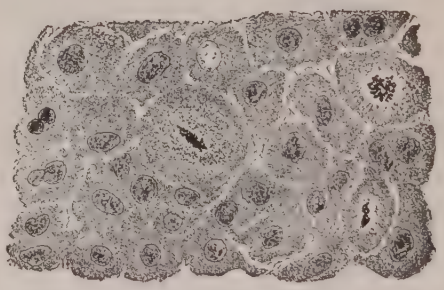


Fig. 236.—Large Round-cell Sarcoma. A tumor of the mamma. Mitotic figures in some of the cells.

nuclei are generally large and contain prominent nucleoli. These neoplasms, like those just described, are often very vascular and contain a variable quantity of basement substance; they are occasionally alveolar in character. As a rule, they are less soft and less malignant than the small-cell type.

Differential Diagnosis.—A small round-cell sarcoma may be distinguished from an inflammatory lymphocytic infiltration by its sharper boundary, as well as by the fact that its cells usually exceed the lymphocyte somewhat in size and are often found in process of division; furthermore, the nuclei are apt to be larger and more vesicular than those of lymphocytes. A leukemic infiltration is not so discrete as a sarcoma, and does not destroy the invaded tissues as a sarcoma does. Nevertheless, an absolute distinction between a small round-cell sarcoma and a lymphocytic infiltration may sometimes be impossible (see also Lymphoblastoma).

Lymphoblastoma (*lymphosarcoma*).—There may occur in any part of the lymphatic system a tumor composed of lymphocytes (*lymphocytoma*) or, more generally, of their ancestral element, the lymphoblast (*lymphoblastoma*). This type of growth is often called a *lymphosarcoma*, but as there is an increasing desire on the part of pathologists to reserve

the term sarcoma for neoplasms of supporting connective tissue, *lymphoblastoma* has been suggested[1] as a substitute.

In metastasizing, the lymphoblastoma characteristically follows the lymph-channels at first, spreading along them from one node or follicle to the next, but it finally invades the surrounding structures also until all are fused into one firm mass. Thus it progresses from one region to another though without ever becoming so generalized as leukemia or pseudoleukemia. Extensive local metastasis of this sort produces the condition known as *lymphosarcomatosis*.[2] Metastasis by way of the blood stream is rare, so that secondary nodules in outlying organs are not commonly encountered.

The parenchyma of an affected node is entirely destroyed, its follicles and lymph-cords being no longer recognizable, while the capsule and surrounding tissues are densely infiltrated by tumor cells, elements resembling in size, shape, and appearance the large mononuclear leucocyte.

Since cells of the lymphocyte class produce no intercellular substance, the only stroma possessed by the lymphoblastoma is such as may be furnished by the invaded tissues.

Differential Diagnosis.—The cells are larger than those of a small round-cell sarcoma. From a large round-cell sarcoma the lymphoblastoma may be distinguished by the lack of a proper stroma,[3] its early limitation to the lymphatic system, the capillary size of its blood-vessels, the absence of hemorrhage, and its tendency to metastasize in organs ordinarily spared by malignant growths.

Plasmocytoma[4] (*plasmoma, plasma-cell myeloma, plasmomyeloma*).—This growth, composed of plasma cells, is closely related to the lymphoblastoma but differs from it in being usually benign. In the bones,[5] however, it may behave as a malignant growth.[6]

For a discussion of **chloroma,** see pages 546 and 1094.

Myeloma.—The myelomata (see page 1094) include a group of peculiar tumors which resemble the sarcomata in many ways, though differing from them in histogenesis. They are derived from the bone-marrow and are usually multiple,[7] appearing as grayish or reddish masses which, in their growth, cause absorption of the bone. Metastasis is rare.[8]

Oxydase reactions may or may not be given by the cells according to the type (myeloblast, myelocyte, lymphocyte, plasma cell, erythroblast) from which the growth springs.[9]

For a discussion of Bence-Jones' protein, often found in the urine in connection with myeloma, see page 1095.

[1] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 364.

[2] *Kundrat*, Wien. klin. Wchnschr., 1893, vi, 211; *Paltauf*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, iii[1], 652; *Sternberg*, ibid., 1903, ix[2], 481.

[3] For a study of the stroma, see *Seelig*, Surg., Gynec., and Obst., 1907, iv, 319 (bibl.).

[4] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 378 (bibl.); *Jessup*, Proc. New York Path. Soc., 1912, xii, 6 (bibl.); *Frank, A.*, Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 115; *Zimmermann*, Virchows Arch., 1914, ccxvi, 214.

[5] *Warstat*, Zieglers Beitr., 1913, lv, 225 (bibl.).

[6] *Versé*, Verhandl. d. deutsch. path. Gesellsch., 1912, xv, 62 (bibl.).

[7] *Hoffman*, Zieglers Beitr., 1904, xxxv. 317 (bibl.); *Christian*, Jour. Exper. Med., 1907, ix, 325.

[8] *Pepper* and *Pearce*, Jour. Med. Research, 1918, N. S. xxxii, 171.

[9] *Vance, B. M.*, Am. Jour. Med. Sc., 1916, clii, 693 (bibl.); *Forman* and *Warren*, Jour. Cancer Research, 1917, ii, 79 (bibl.).

Melanoma.[1]—These tumors arise most frequently in the skin (Figs. 237 and 238) where pigmented moles often form the starting point. The next most frequent site is the choroid, but they also arise in the

Fig. 237.—Melanoma of the Skin, Fungoid in Shape.
A small nodule showing local extension is seen in the subcutaneous tissue beneath.

mucous membranes of the gastrointestinal tract, adrenal, peripheral nerves, meninges and brain.[2] As a rule, the pigment is quite irregularly distributed in patches or streaks in either the spindle or polyhedral cells

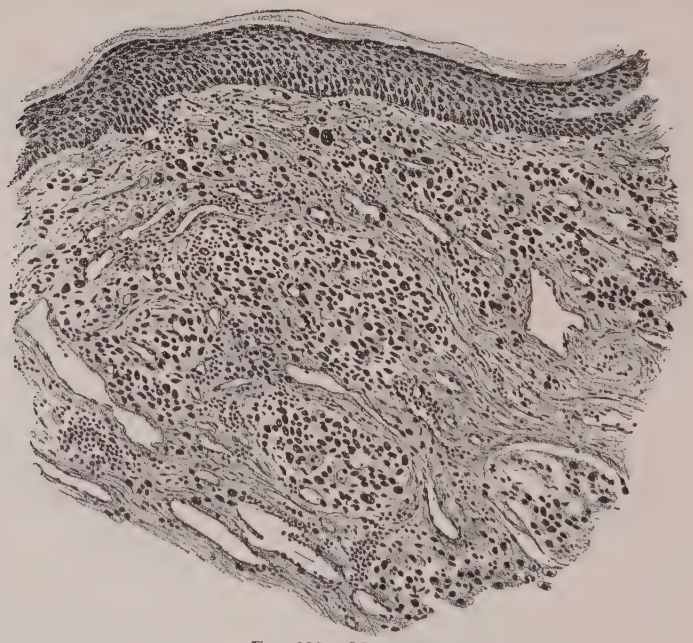


Fig. 238.—Melanoma.

of the tumor, in branched connective-tissue cells (chromatophores) or in the intercellular substance. The pigment varies from a golden brown to

[1] Owing to the confusion which exists as to the nature of these tumors, the name *melanoma* seems best, though *Ribbert* (Zieglers Beitr., 1887, xxi, 471 (bibl.); and Geschwulstlehre, 2d ed., Bonn, 1914, 318; *Ribbert, H.*, Bemerkungen zum Chromatophorom, Centralbl. f. allg. Path., 1918, xxix, 273) prefers to call them *chromatophoroma* and *Lubarsch* has suggested the name *melanocytoblastoma.*

[2] *Omodei-Zorini*, Virchows Arch., 1924, ccl, 566 (bibl.).

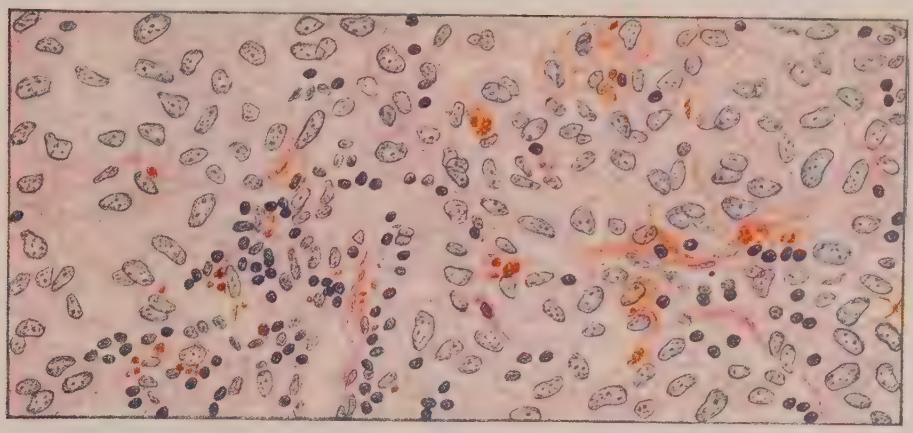


FIG. 1. MELANO-EPITHELIOMA FROM PIGMENTED MOLE

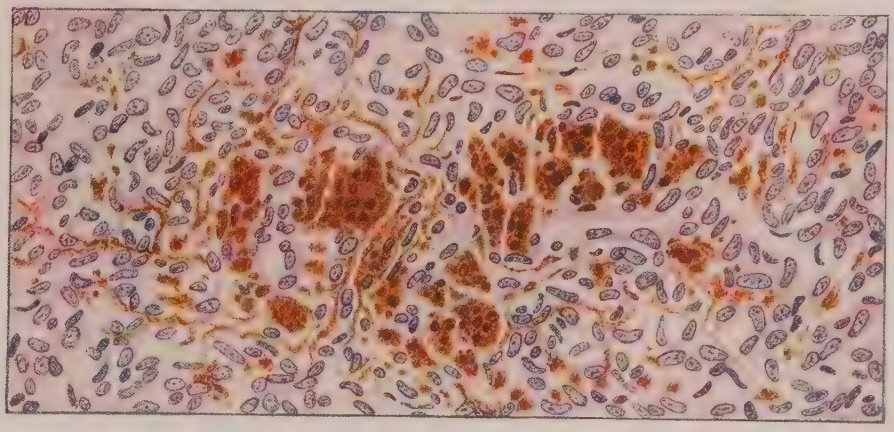


FIG. 2. PRIMARY MELANOSARCOMA OF NERVE TRUNK.

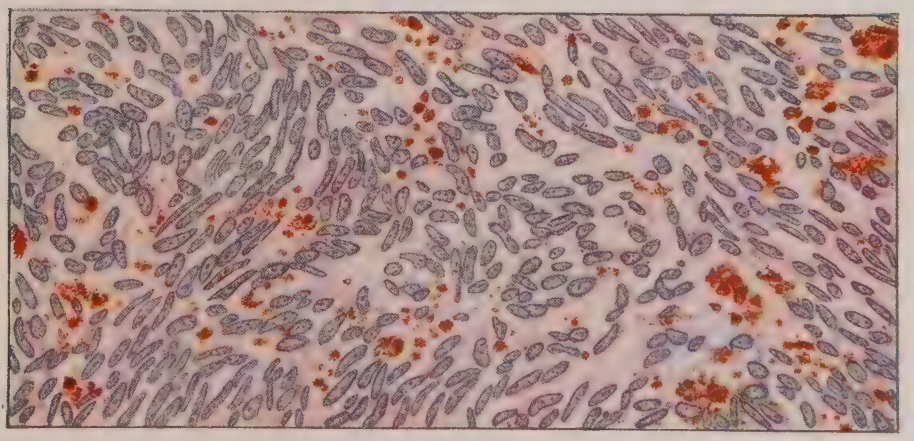


FIG. 3. MELANOSARCOMA OF CHOROID OF EYE.

black, the latter color being most frequent in the choroid tumors. Microscopically, the pigment may be fine or coarse, and varies greatly in amount in the cells of the tumor. In some it may be so abundant as to wholly mask the cell structures, in others a few fine brownish granules are all that can be seen. Two types of cells are found forming the parenchyma of the melanomata. The most frequent is a large polyhedral cell, with one or more nuclei resembling epithelium, but without the intercellular bridges of mature squamous cells. Less often the main bulk of the tumor is made up of spindle cells similar to those found in the sarcomata. The melanomata[1] are highly malignant, metastasize both through the lymphatics and the blood vessels, and are resistant to radiation therapy. They form metastases in various parts of the body, which, like the parent tumors, are deeply pigmented, moderately so, or even entirely free from pigment. Such metastases are very frequent in the liver and a jet-black nodule may lie in juxtaposition with one which is perfectly white. Melanotic pigment is excreted in the urine, giving rise to melanuria.[2] Such melanuria is not, however, necessarily proof of the existence of a melanotic tumor in the body. The dominant opinion at present is that most of the pigmented tumors of the skin are epithelial in origin and that the chromatophores are connective-tissue cells which have phagocyted pigment formed by the epithelium. The alveolar arrangement, the lack of connective tissue fibrils from between the cells, the occasional presence of keratin,[3] are regarded as conclusive arguments. Those of the eye and nervous system are presumably of mesodermic origin. Recently Masson[4] has brought forward some evidence to show that the pigmented tumors of the skin are neural in their derivation and result from the proliferation of the nerve and other structures in the terminal buds of the sensory nerves.

Differential Diagnosis.—Various forms of neoplasm may contain brownish or yellowish pigment, deposited in them by degeneration of the hemoglobin from extravasated blood; these should not be mistaken for melanotic sarcomata. Blood pigment is not so dark as melanin and is generally included in phagocytic cells lying in the stroma; a careful search will in many cases reveal crystal or needle forms, and an iron reaction can usually be obtained by treating sections with acid and potassium ferrocyanide. The granules of black pigment sometimes seen in tissues fixed with formalin are so fine that they can hardly be mistaken for melanin; furthermore, they are soluble in dilute ammonia water.

Giant-cell Sarcoma.[5]—Growths of this class, which originate most often in the marrow (*myeloid sarcoma*) of the femur, tibia and radius, and less

[1] *Dawson*, The melanomata, Edin. Med. Jour., 1925, xxxii, 501.

[2] For details concerning our present knowledge of melanin and melanuria see *Wells*, Chemical Pathology, 5th ed., Philadelphia, 1925, Chapter XX.

[3] *Beckey*, Frankfurt. Ztschr. f. Path., 1915, xvii, 365 (bibl.).

[4] *Masson, P.*, Ann. d'Anat. Path., 1926, iii, 417, 657.

[5] There is no problem in the whole subject of tumor pathology which has been more discussed of late than the exact classification of the nature of tumors of this group. Some excellent pathologists hold that they are all benign, but there is considerable evidence that occasionally a tumor of this type may occur which is malignant and may metastasize. A very fair survey of the X-ray diagnosis, morphology and treatment of these tumors may be found in a monograph on bone sarcoma by *Kolodny*, published as a supplement to Surgery, Gynecology and Obstetrics, 1927, pages 172 to 214.

commonly in the periosteum, are composed of fusiform or spheroidal cells of various sizes, interspersed more or less thickly with multinucleated giant cells (Fig. 239); no bone is formed, as a rule, wherein these differ from the true osteosarcomata, tumors of the bone itself.

While giant cells may be occasionally discovered in almost any kind of growth, they are most abundant and characteristic in the lesion now under discussion. Here the situation of their nuclei is most commonly central rather than peripheral, whereas in the giant cells characteristic of tuberculosis (*Langhans type*) they are apt to occupy a position at one

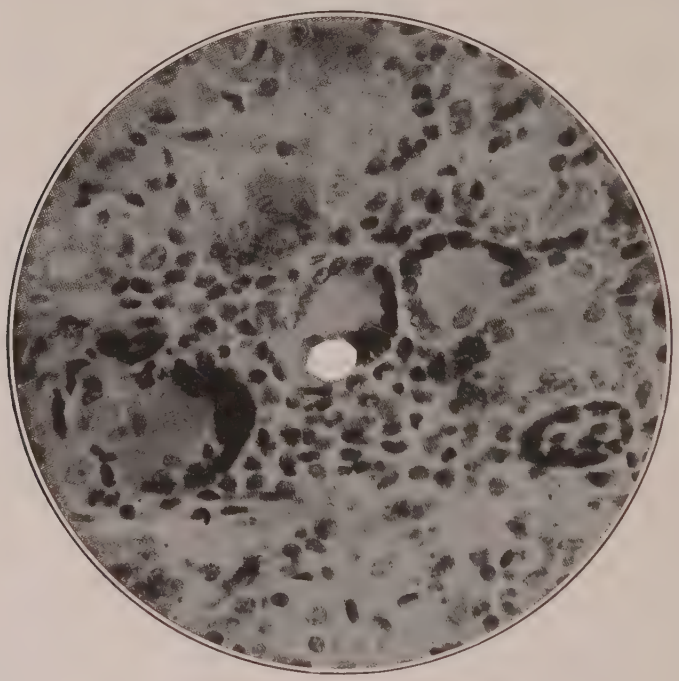


FIG. 239.—GIANT-CELL SARCOMA OF FINGER.
Periosteal type.

end of a somewhat elliptical cell body; in foreign body giant cells their distribution is irregular and they may be found at one end, at both ends, or gathered about any foreign body with which the cell is in contact. Mitotic figures are occasionally seen in the nuclei of giant cells of rapidly growing and recurrent tumors (Fig. 240).

This giant-cell lesion of the bone-marrow is subject to hemorrhage and is sometimes so soft and vascular that it may be mistaken for an aneurysm;[1] its appearance is usually compared with that of currant jelly. It is so slightly malignant that simple curettage of the bone often suffices to cure it.[2] Indeed, so little does it resemble the sarcomata as

[1] *Gaylord*, Ann. Surg., 1903, xxxvii, 834; *Nakayama*, Beitr. zur klin. Chir. (Bruns), 1909, lxiv, 524.
[2] *Bloodgood*, Trans. Am. Surg. Assn., 1912, xxx, 463.

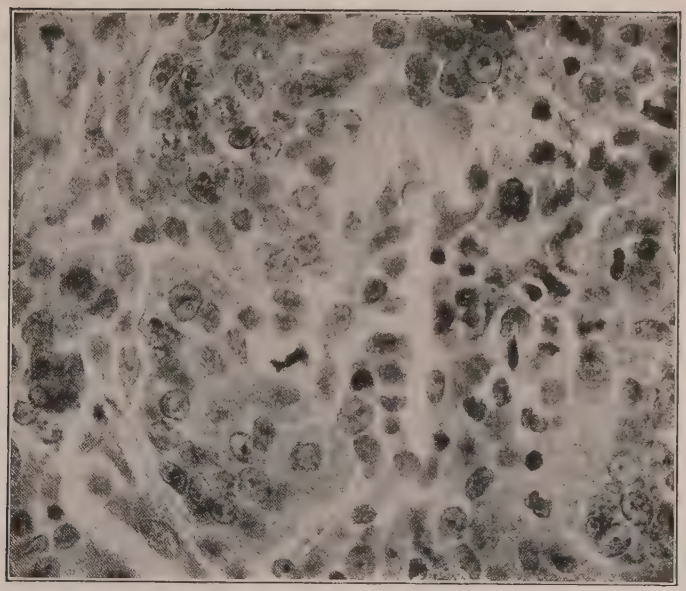


FIG. 240.—GIANT-CELL SARCOMA OF SUPERIOR MAXILLA.
Fifth recurrence. Mitosis in giant cell.

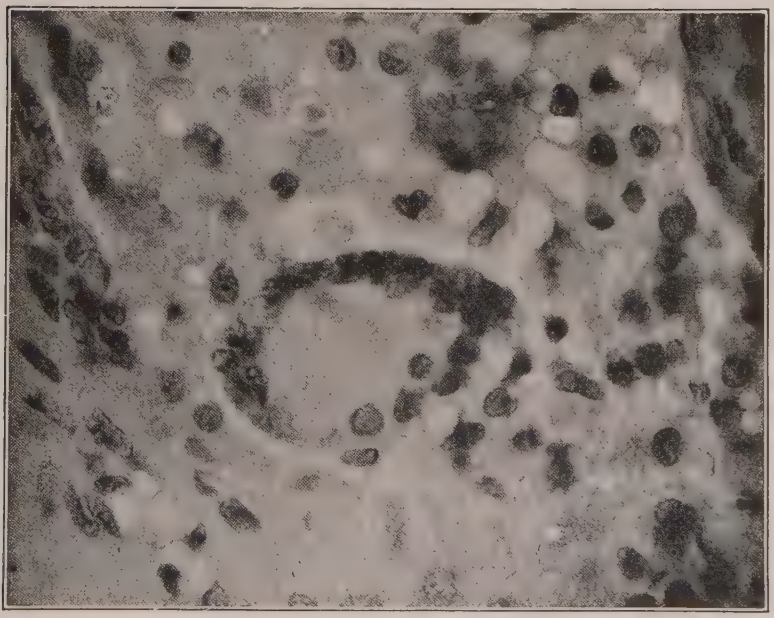


FIG. 241.—EPULIS OF GUM.
Showing the Langhans' type of giant cell seen in these growths, also the spongy soft connective tissue in which the cells lie. Numerous leucocytes and red blood-cells are seen in the section.

to virulence, that it is regarded by some observers as a simple inflammatory lesion[1] or as a benign growth.[2]

An example of the periosteal type of giant-cell sarcoma is one variety of *epulis*, a clinical term including all tumors about the gums (Fig. 241). This growth, which arises from the periosteum of the maxillary border, is generally quite harmless if carefully removed; thus, in one series only two recurrences were noted in seventy cases. If excision be imperfectly performed, however, repeated local recurrences may take place, though without metastases appearing anywhere in the body.

A benign giant-cell sarcoma occurs also about the tendons and aponeuroses of the hand and foot.[3]

Fig. 242.—Osteoid Sarcoma.
Metastasis in lung.

Osteosarcoma.—In contrast to the myeloid sarcoma, which develops from the marrow cavity, the osteosarcoma is without any doubt a true neoplasm, since it invades the surrounding parts, metastasizes (Fig. 242), and usually proves fatal within a comparatively short time. It originates

[1] *Barrie*, Ann. Surg., 1913, lvii, 244; *Barrie* and *Hillman*, Surg., Gynec., and Obst., 1914, xix, 42.

[2] *Adami*, Principles of Pathology, 2d ed., Philadelphia, 1910, i, 734; *Bland-Sutton*, Tumors Innocent and Malignant, New York, 1917, p. 45.

For a brief discussion of this question, see *Martland*, Proc. New York Path. Soc., 1915, xv, 119; and *Haussling* and *Martland*, Ann. Surg, 1916, lxiii, 454.

[3] *Spiess*, Frankfurt. Ztschr. f. Path., 1913, xiii, 1 (bibl.).

occasionally in the soft parts,[1] but more often in the bone itself, usually within the shaft (*central sarcoma*) or from the outer surface (*peripheral sarcoma*); both these are called *endosteal* to distinguish them from a third class which arises in the periosteum (*periosteal sarcoma*). The structure and the clinical course are the same, however, in all true osteosarcomata arising in the skeletal system. The bones most commonly affected are the long bones, of which the femur is most often involved; next follow in order the tibia and the humerus.

Osteosarcomata are spindle-cell or round-cell tumors containing masses of bone; this is usually atypical in structure, the regular lamellations and Haversian canals being generally absent (Fig. 243). Not infrequently, calcification is imperfect or lacking (*osteoid tissue*).

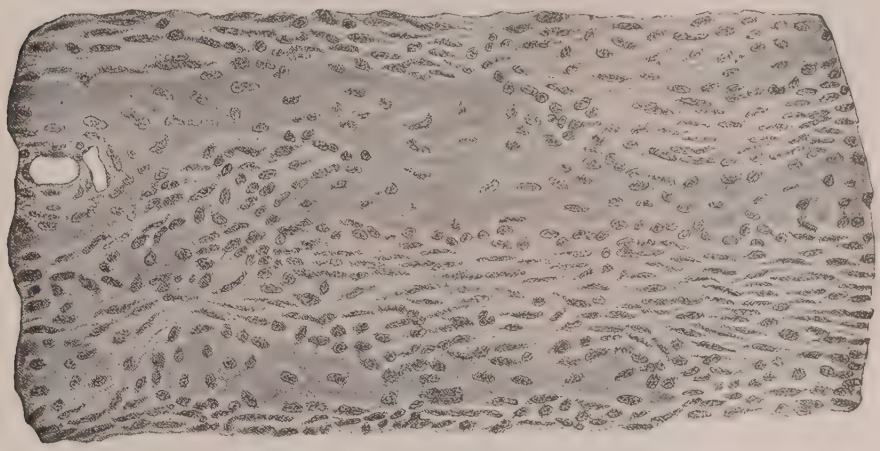


Fig. 243.—Osteosarcoma of Leg.

Bone sarcomata are said to have been preceded in some instances by osteitis deformans (Paget's disease of bone);[2] but it has been said also that patients with this type of osteitis are apt to develop carcinoma. It should be remembered, in any case, that most of the subjects of Paget's disease of the bone are in the cancer age, and some doubt may therefore be expressed regarding the value of these assertions pending the collection of an adequate statistical material. There is also the possibility that those cases of supposed Paget's disease in which sarcomata are said to have developed, were actually cases of osteitis fibrosa, some forms of which are distinguished only with difficulty from sarcomata, and other types of which are prone to develop into sarcomata.

Fibrosarcoma.—In the fibrosarcoma collagen is the intercellular material elaborated. Sometimes there is so much that the growth may appear at first sight to be merely a rather cellular fibroma, but closer examination of such a neoplasm will reveal irregularities in the size of the nuclei and in the size and staining properties of the cell bodies, while

[1] For bibl., see *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 276.
[2] For bibl., see *Heaslit*, New York State Jour. Med., 1917, xvii, 330.

mitotic figures are apt to be more abundant than in the fibroma (see page 398). In a few cases, the diagnosis will be difficult or impossible.

Angiosarcoma.—One type of neoplasm to which this term is frequently applied is a rather vascular sarcoma which has undergone necrosis save for several layers of cells bordering the blood-vessels; these remain alive because they are nearest to the food supply (Fig. 244, 245, and 246). But the preservation of cells favorably situated, in the face of an otherwise general necrosis, may be a feature of the carcinomata and of many

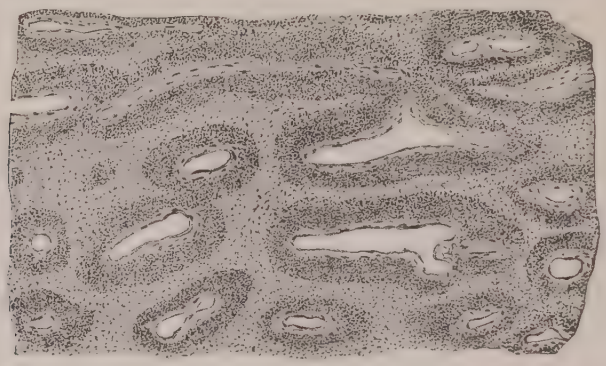


FIG. 244.—VASCULAR SARCOMA.
Tumor from the arm. Sometimes called angiosarcoma or perithelial sarcoma.

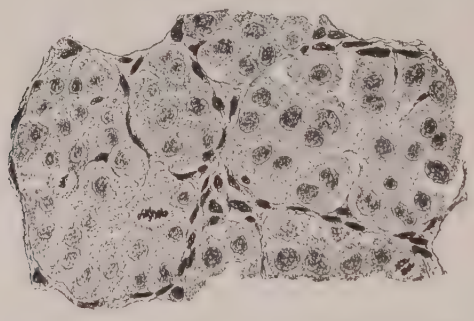


FIG. 245.—VASCULAR OR ANGIOSARCOMA OF LYMPH-NODE (ENDOTHELIOMA?).

other tumors, and no good reason appears why this condition should be used as a basis for classifying the sarcomata.

Another sarcoma frequently referred to as angiosarcoma is that variety in which the vessels are prominent by reason of their great number rather than their isolation in consequence of a wide-spread necrosis. But to merit the name angiosarcoma a tumor would have to originate from the endothelium of a vessel, and doubt has been expressed[1] whether there actually is such a growth; nor has the term *perithelial sarcoma*, sometimes applied to those neoplasms in which the vessels are surrounded by a mantle of tumor cells, fared any better.[2]

[1] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 262.
[2] *v. Hansemann*, Ztschr. f. Krebsforsch., 1905, iii. 234.

If the need be felt of qualifying the simple designation sarcoma, it would therefore be better, on the whole, to replace the name angiosarcoma with some such term as *vascular sarcoma*.

Alveolar Sarcoma.—Sometimes the connective-tissue framework of a sarcoma, particularly in the round-cell varieties, is abundant and assumes the form of a network containing the tumor cells within its meshes. The spaces are called *alveoli*, and this variety of neoplasm has acquired importance because it imitates the well-defined alveolar arrangement characteristic of many of the carcinomata. Growths of this kind are not common, but may occur in the skin, lymph-nodes, bone, and pia mater. They are usually very malignant.

Fig. 246.—Vascular or Angiosarcoma of Humerus (Endothelioma?).

Differential Diagnosis.—An alveolar sarcoma may be confused with a carcinoma. In the sarcoma, however, there is a more intimate relation between the cells and their stroma—that is to say, the connective tissue sends out trabeculæ which pass into the alveoli and between the individual cells. But a careful study of sections especially prepared to show these fine fibrils, by Bielschowsky's silver method, for example, or by shaking in water to dislodge loose cells, may be required to distinguish one of these growths from the other. In the carcinoma, no connective-tissue fibrils are to be found between the cells, and, being unsupported, these are readily washed out when the section is shaken in water.

Mixed Forms of Sarcoma.—In addition to the more or less well-defined forms of sarcoma which have now been briefly presented, there exist various others, such as the *liposarcoma*, which contains fat; the

chondrosarcoma, which contains cartilage; the *chondro-osteosarcoma*, etc. Certain modifications also have received special names; thus, sarcomata in which cysts form through degeneration, or the dilatation of alveoli or ducts by pressure, have received the name *cystosarcoma*. Mucous degeneration is frequent, and a combination of myxoma and sarcoma (*myxosarcoma*) is common (Fig. 247). A mixture of adenoma and sarcoma (*adenosarcoma*)[1] is rare in adult life, the ordinary adenosarcoma being a congenital tumor of the kidney in children.[2] The terms *myosarcoma* and *gliosarcoma* many authors[3] would replace with *malignant myoma* and *malignant glioma*, reserving sarcoma as a designation solely for tumors of connective tissue.

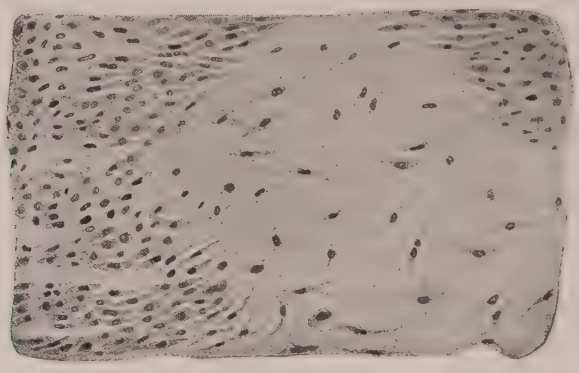


FIG. 247.—MYXOSARCOMA OF PAROTID.

Sarcoma is sometimes combined with carcinoma, some twenty-five cases having been reported in man.[4] In mice, however, the combination is not so rare;[5] here the sarcoma is supposed to arise secondarily in the stroma of a carcinoma, possibly because the cells of the latter exert some sort of irritant action upon the connective tissue. This hypothesis is strengthened by the study of certain transplantable carcinomata whose cells have the power to induce a sarcomatous alteration in the stroma, and it has been found that from one to three months' growth in any one animal is required for the change to be brought about. It is very probable that carcinosarcoma of the human subject, hitherto so puzzling, can be explained in the same way. It should be added, however, that certain observers, and notably Krompecher, regard the entire growth as an epithelial tumor in which the cells in certain areas have assumed a spindle shape.[6]

[1] *Wengraf*, Virchows Arch., 1913, ccxiv, 161 (bibl.); *Trappe*, Frankfurt. Ztschr. f. Path., 1907, i, 130 (bibl.).

[2] The term has been applied by *Beneke* (cited by Kaufmann, Lehrbuch der spez. path. Anat., Berlin, 1911, ii, 802) to malignant tumors of the adrenal.

[3] *e.g.*, *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 434.

[4] *Herxheimer*, Zieglers Beitr., 1908, xliv, 150; *Saltykow*, Centralbl. f. allg. Path., 1914, xxv, 419.

[5] *Ehrlich*, Ztschr. f. Krebsforsch., 1907, v, 62; *Apolant*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d ed., 1913, iii, 167; *Haaland*, Third Sci. Report, Imperial Cancer Research Fund, London, 1908, p. 175; *Russell*, Jour. Path. and Bacteriol., 1910, xiv. 344. For a complete review of the cases up to 1913, see *Woglom*, The Study of Experimental Cancer, New York, 1913.

[6] For a discussion of this question, see *Woglom*, Jour. Cancer Research, 1918, iii, 47.

ENDOTHELIOMA.

No class of new growths has given rise to so much controversy and yet remained so indefinite as this one. There is, in fact, hardly an obscure tumor that has not at one time or another, since the appearance of Volkmann's monograph,[1] been called an endothelioma.

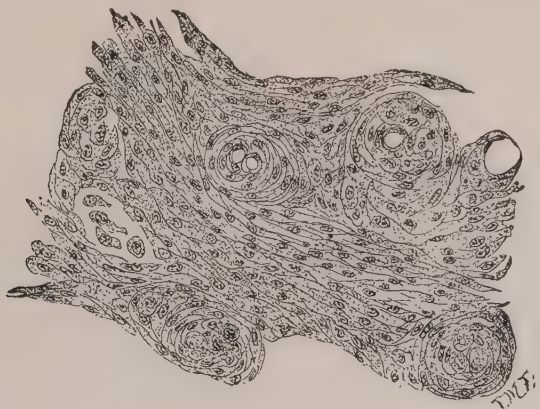


Fig. 248.—Endothelioma (Endothelial Sarcoma) of Dura Mater.

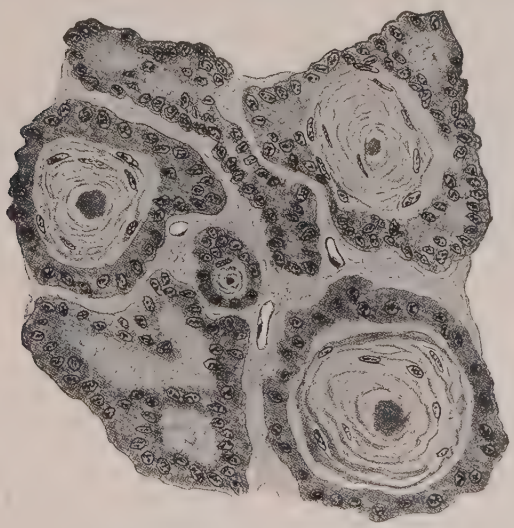


Fig. 249.—Endothelioma of Dura Mater.
Psammomatous form.

If this diagnosis is to be made, however, the origin of the neoplasm from endothelium—that is, from blood- or lymph-vessels—must be demonstrated, and Ribbert[2] demands further that the cells show a tendency to form such vessels. In short, he regards it as extremely probable

[1] *Volkmann*, Deutsch. Ztschr. f. Chir., 1895, xli, 1. For a full discussion of the endothelioma, see *Marchand*, Verhandl. d. deutsch. path. Gesellsch., 1900, ii, 38.

[2] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 243.

that, apart from the psammoma of the dura mater (Fig. 248, 249, and 250), which he accepts as an endothelioma,[1] there is in the long run no endothelioma but the angioma. Yet he does not deny absolutely the possibility that endothelium may occasionally grow in solid masses, and cites a case[2] to show that it may give rise to a tumor resembling a sarcoma both clinically and morphologically. It is interesting to find, however, that in the younger parts of even this neoplasm Colmers[2] described a distinct tendency toward the elaboration of vessels. The benign endothelioma of the pulmonary vein reported by Sailer,[3] is perhaps another authentic example of endothelioma of the solid type.

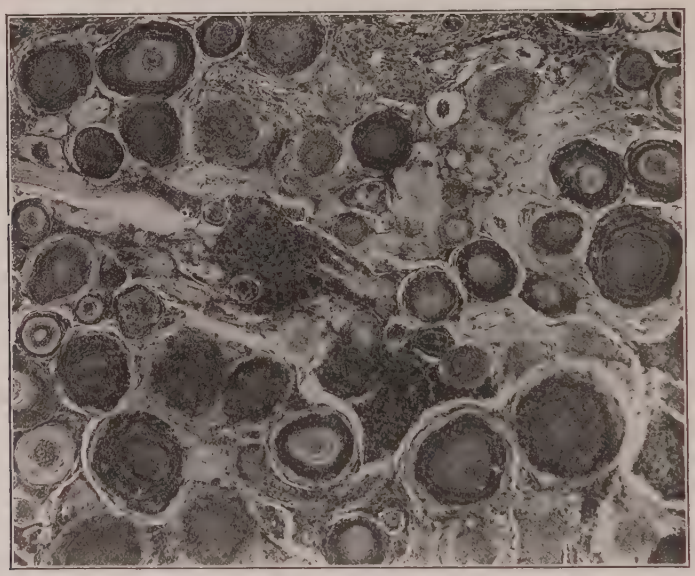


Fig. 250.—Endothelioma of Dura Mater.
Psammomatous form.

While all authorities are not so radical[4] as Ribbert, a large number of new growths have nevertheless been dismissed in recent years from among the endotheliomata. For example, that neoplasm which sometimes arises in the pleura[5] is now often called *mesothelioma* (Fig. 251), since the lining cells of the pleura, peritoneum, and pericardium are no longer universally regarded as endothelium,[6] but if this tumor could be shown to develop, not from the superficial layer (*mesothelium*) but from the pleural lymph-channels, as some observers assert that it does, the name endothelioma

[1] See *Prym*, Virchows Arch., 1914, ccxv, 212, for a discussion of this question.

[2] *Colmers*, Zieglers Beitr., 1903, xxxiv, 295 (bibl.).

[3] *Sailer*, Contributions from the William Pepper Laboratory of Clinical Medicine, 1900, University of Pennsylvania (abstr., Centralbl. f. Path., 1901, xii, 263). A somewhat similar case is that of *Unruh*, Deutsch. med. Wchnschr., 1896, xxii, 746.

[4] *e.g.*, *Adami*, Principles of Pathology, 2d ed., Philadelphia, 1910, i, 813.

[5] *Rosenbaum*, Ztschr. f. Krebsforsch., 1914, xiv, 543 (bibl.).

[6] See *Minot*, Science, 1901, xiii, 481; *Miller* and *Wynne*, Jour. Path. and Bacteriol., 1908, xii, 267; *Mönckeberg*, Zieglers Beitr., 1903, xxxiv, 489; *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 240; *Benda*, Deutsch. med. Wchnschr., 1897, xxiii, 324.

would have to be retained. Another type of growth to be excluded from the endotheliomata is the mixed tumor of the salivary glands, which is regarded by most authorities[1] as epithelial.

The difficulties which stand in the way of a thorough conception of the endotheliomata may be illustrated as follows: A recent author[2] distinguishes *lymphangioendothelioma* and *hemangioendothelioma*, the latter

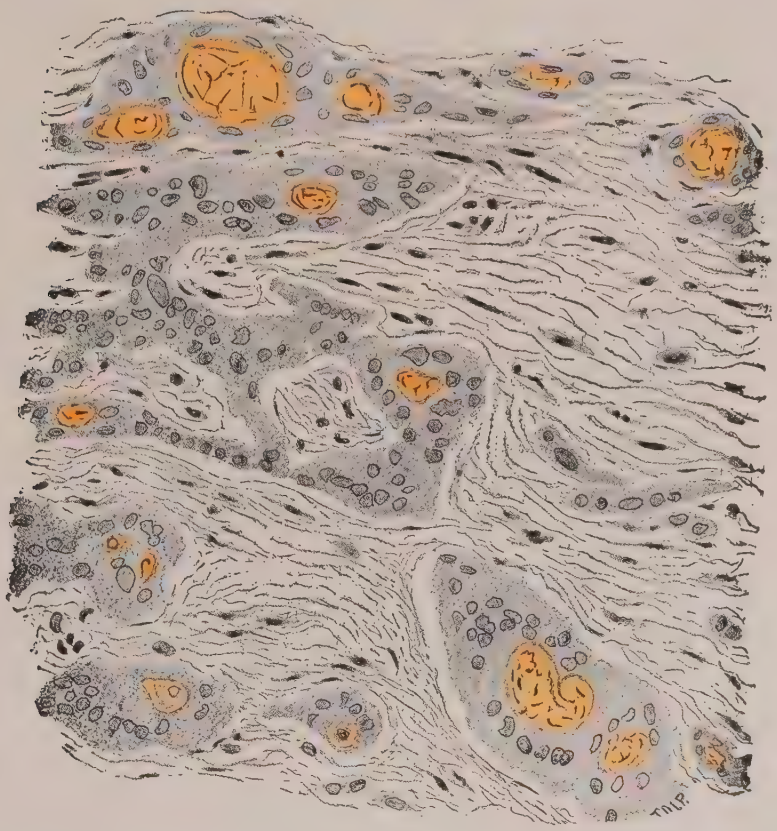


FIG. 251.—MESOTHELIOMA OR "ENDOTHELIAL CANCER" OF PLEURA.
Showing the formation of mucus within the endothelial-cell masses; the mucus is stained with hematoxylin.

of which is divided into the *endothelioma*, originating inside the vessel, and the *perithelioma*, arising from the *perithelium* at its periphery. A second[3] doubts the very existence of perithelium; a third[4] asserts that perithelium is to be found about the blood-vessels of the brain and a few other organs; while a fourth writer,[5] finally, is loath to acknowledge any neoplasm as an endothelioma.

[1] *Wood, F. C.*, Ann. Surg., 1904, xxxix, 57: *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 601; *Wilson* and *Willis*, Am. Jour. Med. Sc., 1912, cxliii, 656 (bibl.).
[2] *Borst*, in Aschoff's Pathologische Anatomie, Jena, 1913, p. 719.
[3] *MacCallum*, Textbook of Pathology, Philadelphia, 1916, p. 934.
[4] *von Hansemann*, Ztschr. f. Krebsforsch., 1905, iii, 245.
[5] *Fick*, Monatsh. f. prakt. Dermat., 1909, xlviii, 104.

Epithelial Tumors—Benign.

Since even normal epithelium varies greatly in its morphology, that of the pulmonary alveoli, for example, looking like endothelium, it may readily be imagined that under abnormal conditions epithelium will sometimes prove difficult of recognition. Thus the epithelium in mixed tumors of the parotid gland is so atypical that there are still those who would derive these growths from the connective tissues; again, it has been asserted[1] that the tumor regarded by most pathologists as a carcinosarcoma is really a pure carcinoma, its spindle-shaped cells being epithelium in spite of their morphological resemblance to the fibroblast; or, to cite a third instance, a medullary carcinoma may closely resemble a sarcoma.

But epithelium has certain characteristics, one or more of which can usually be discovered by careful search or by the employment of special staining methods, so that in the long run the number of tumors that remain persistently in the doubtful class will be small. The presence of

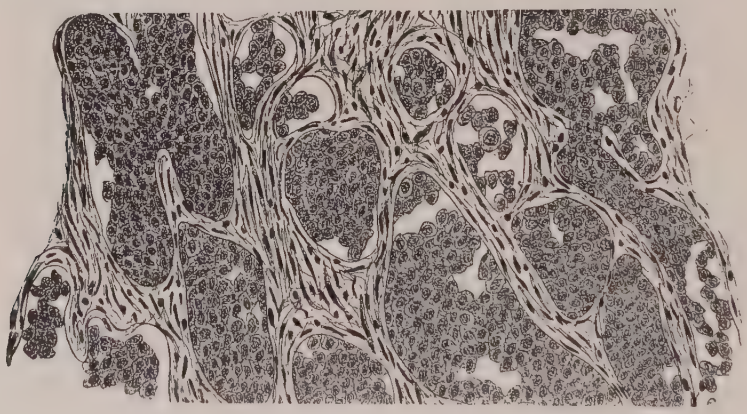


Fig. 252.—Medullary Carcinoma of Stomach.
Carcinoma Molle.

keratinization, for example, or of intercellular bridges, is reliable evidence that the neoplasm originated in surface epithelium, while indications of a glandular arrangement point to the epithelium of some gland as the site of inception. In a certain number of cases, however, all such clues will be absent, and recourse must be had to special methods which will stain the finer strands of connective tissue. If these fibrils can be found between individual cells, the neoplasm under examination may be declared a connective-tissue growth; if not, it is equally certain that the tumor is of epithelial origin.

Unlike the sarcomata, the epithelial neoplasms have in most cases a prominent connective-tissue stroma; this, however, takes no part in the activities of the tumor (unless in those few growths regarded by Ribbert as fibroepithelial), but forms a mere scaffolding to support the paren-

[1] *Krompecher*, Zieglers Beitr., 1908, xliv, 88.

chyma and conduct its blood-vessels. It is entirely passive, being formed from the surrounding connective tissues at the behest of the epithelial portion of the neoplasm. The stroma may be sparse or abundant, may contain few cells or many, is sometimes arranged in fascicles or bands, and frequently forms the wall of well-defined spaces of various shape called *alveoli* (Fig. 252) within which lie the epithelial cells forming the parenchyma.

As with the connective-tissue new growths, epithelial tumors may be divided into *mature*, or *benign*, and *immature*, or *malignant*. But it must be remembered that the distinction cannot always be made in practice, for there is no infallible morphological criterion of malignancy. All we know is that experience has shown certain histological features to be associated with clinical malignancy. Yet these may be absent and the tumor nevertheless be malignant; there are new growths of the thyroid, for example, which exhibit an absolutely benign structure when regarded from the histological standpoint, but which are nevertheless quite the equal of many carcinomata in their destructive growth and their tendency to metastasize (see page 388).

Bearing these qualifications in mind we may enter upon a discussion of the benign epithelial neoplasms.

PAPILLOMA.

This growth is composed of connective-tissue prolongations covered by epithelium (Fig. 253). The nasal polyp (Fig. 254) also answers this definition, but the following distinction has been drawn between the two types.[1] The nasal polyp is merely a pure fibroma covered with a layer of mucous membrane, while the papilloma is a tumor in which both the connective tissue and the epithelial portions proliferate. For this reason the latter is sometimes called a *fibroepithelial* tumor.

The papilloma of the skin, or common *wart* (*verruca vulgaris*), consists of a connective-tissue stalk covered by thick epithelium; in vertical section it has the outline of a similar section through a cauliflower, on account of the irregularities of its surface. Fissures in the epithelium may admit a few microorganisms, and the stroma, owing to the resulting infection, may be more cellular than is ordinarily the case.

If the epithelium does not wear away as it is formed, which it usually does, a *cutaneous horn* (*cornu humanum*), which may be several centimeters in length, is the result.

For a description of the *venereal wart*, or *condyloma*, see page 927.

Papillomata are common in the bladder and intestine, where they appear as the familiar *polyp*. Here the connective-tissue processes are longer than in the skin, and the tumor assumes a tree-like form. As polyps sometimes undergo malignant change,[2] the pathologist should

[1] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 473.

[2] *Ribbert*, Das Karzinom des Menschen, Bonn, 1911, pp. 164, 400 (bibl.); *Hauser*, Cylinderepithel-Carcinom des Magens u. des Dickdarms, Jena, 1890; *Versé*, Arb. a. d. path. Inst. zu Leipzig, 1908, i, No. V; *Buerger*, Surg., Gynec., and Obst., 1915, xxi, 179; *Syring*, Beitr. z. klin. Chir. (Bruns), 1911, lxxiii, 66 (bibl.).

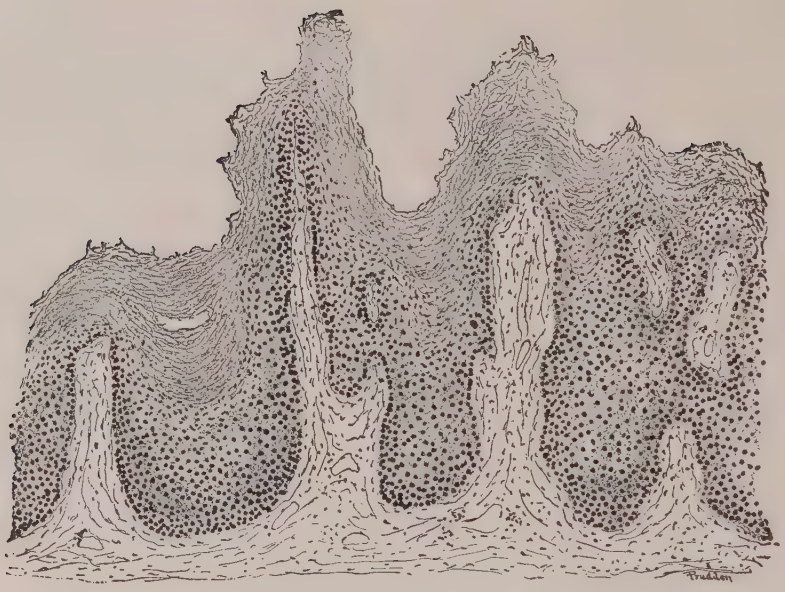


Fig. 253.—Small Papilloma of Skin.

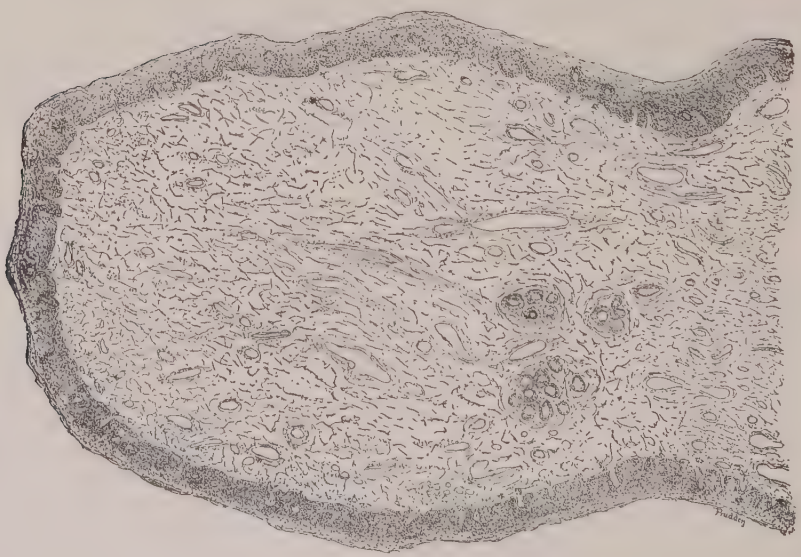


Fig. 254.—Mucous Polyp (Soft Fibroma) of Nose.
The section shows the epithelial covering of the fibroma as well as its numerous blood-vessels and a few mucous glands.

always examine the stalk at its base, where evidences of invasion of the normal tissue will be manifest if the growth has ceased to be benign.

NÆVUS.

The *nævus* (Fig. 255), or *mole*, might be included with equal justice among the connective-tissue new growths, for its true nature is still unknown. Classed by many eminent observers[1] with the epithelial tumors, it is regarded by not a few equally good authorities[2] as originating in the connective tissues; a minority, finally, believe it of neural origin.[3]

The nævus is a flat (*sessile*) or projecting (*pedunculated*) tumor which may or may not be pigmented, covered by epithelium and composed of

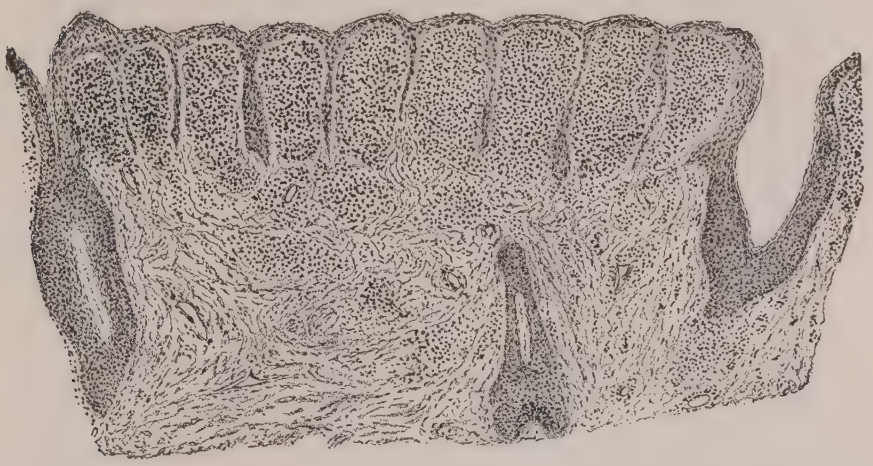


FIG. 255.—A PORTION OF A CONGENITAL NÆVUS OF THE SKIN.

Such small nævi are sometimes mistaken for epitheliomata and occasionally afford a starting-point for the latter.

strands of connective tissue interspersed with columns of *nævus cells*. These are round or oval structures with a comparatively large nucleus, and charged more or less heavily with granules of a dark brown, iron-free pigment (*melanin*). Besides these, the nævus contains a variable number of branched cells (the *chromatophore*, *melanoblast*, or *chromatoblast*) containing melanin and similar to those found in normal pigmented skin. Ribbert contends that the nævus cell is but an early stage of the chromatophore, becoming pigmented and branched as its differentiation proceeds; and that the nævus is a connective-tissue neoplasm, since the chromatophore is a connective-tissue cell. Nævi consisting almost entirely of chromatophores have been described.[4]

[1] *Unna*, Berl. klin. Wchnschr., 1893, xxx, 14; and *Krompecher*, Der Basalzellenkrebs, Jena, 1903, p. 100.

[2] *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 344.

[3] *Masson, P.*, Annal. d'Anat. Path., 1926, iii, 417 and 657.

[4] *Tièche*, Virchows Arch., 1906, clxxxvi, 212.

ADAMANTINOMA.

(*Cystadenoma adamantinum; epithelioma adamantinum*).[1]

This is a rather uncommon tumor which develops at the root of a tooth in the posterior portion of the inferior maxilla, appearing as either a solid or a cystic growth; it is rarely found in the upper jaw.

It is composed of solid or cystic anastomosing alveoli separated by fibrous connective tissue (Fig. 256). The epithelial cells at the periphery of the alveoli are cylindrical, while those toward the center exhibit the

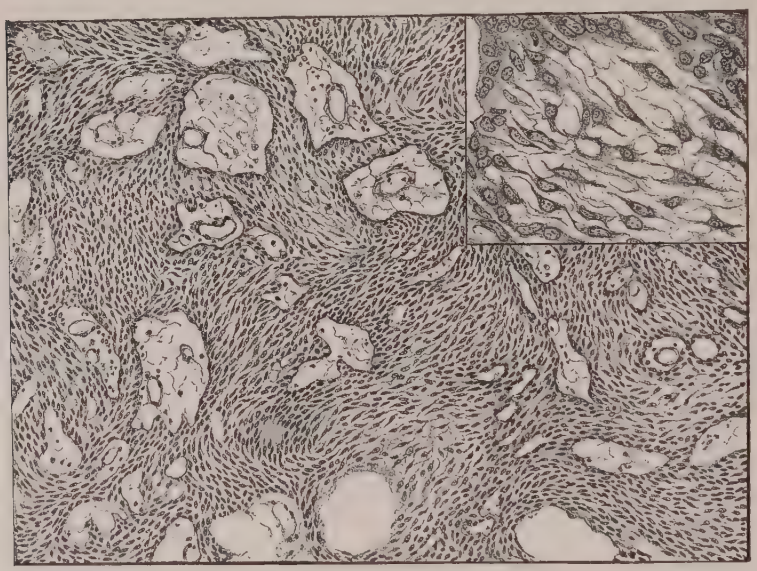


FIG. 256.—ADAMANTINOMA.

stellar shape characteristic of cells of the enamel organ, from remnants of which these growths arise. The stroma may contain bone.

A remarkable pathological curiosity was reported not long since in the shape of a primary adamantinoma of the tibia,[2] which was explained as having developed from a heterotopic tooth anlage.

CYLINDROMA.

Tumors in which homogeneous or striated cylinders of hyaline or mucoid material (Fig. 257), often closely surrounded by layers of cuboidal or flattened cells (Fig. 258), form a striking feature, are called "*Cylindromata.* Some of these growths are carcinomata.

[1] *Chibret*, Arch. de méd. exper., 1894, vi, 278; *Borst*, Die Lehre von den Geschwülsten, Wiesbaden, 1902, p. 605; *Malassez*, Les débris épithéliaux paradentaires, Paris, 1910; *Kuru*, Centralbl. f. allg., Path., 1911, xxii, 291; *L'Esperance*, Proc. New York Path. Soc., 1910, x, 136.

[2] *Fischer*, Frankfurt. Ztschr. f. Path., 1913, xii, 422.

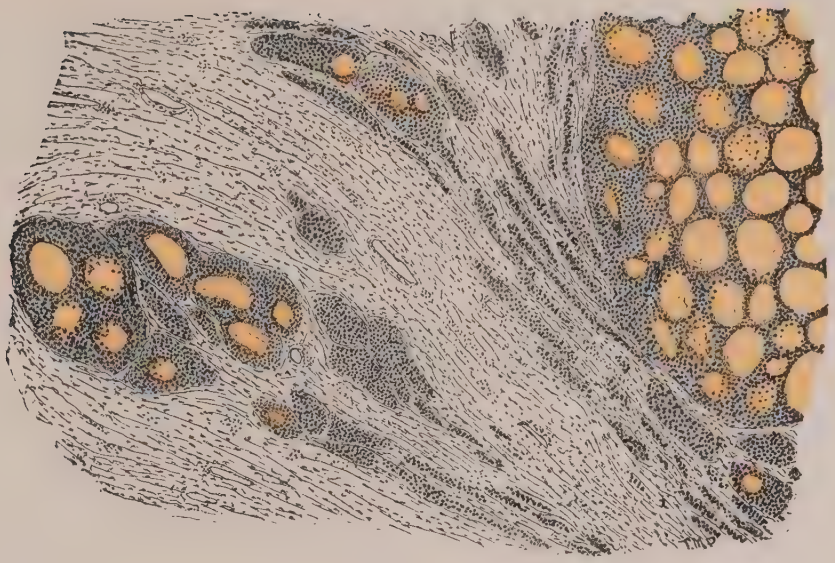


FIG. 257.—CYLINDROMA OF UPPER JAW.
Showing the formation of mucus in the gland-like epithelial masses

FIG. 258.—BASAL-CELL EPITHELIOMA OF ANTRUM.
There is a tendency to the formation of glands, and hyaline or mucoid material like that shown in Fig. 257 is not infrequently present.

ADENOMA.

The adenoma (Fig. 259) is a tumor of glandular epithelium, in which epithelium and connective tissue grow coordinately. Hence, the relative proportion of parenchyma and stroma corresponds approximately to that characteristic of the organ from which the neoplasm is derived, and the

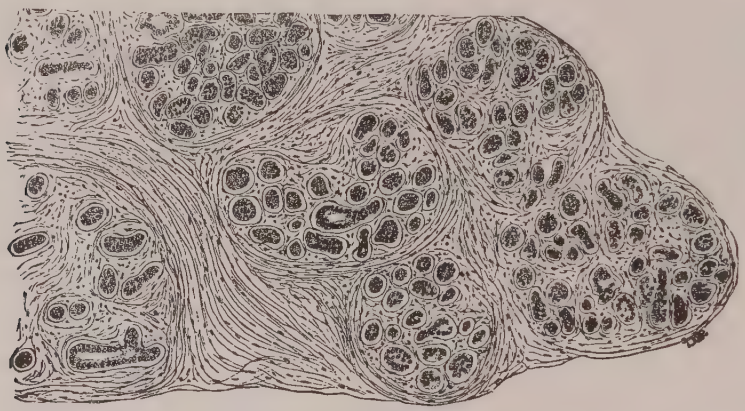


FIG. 259.—ADENOMA OF MAMMA.

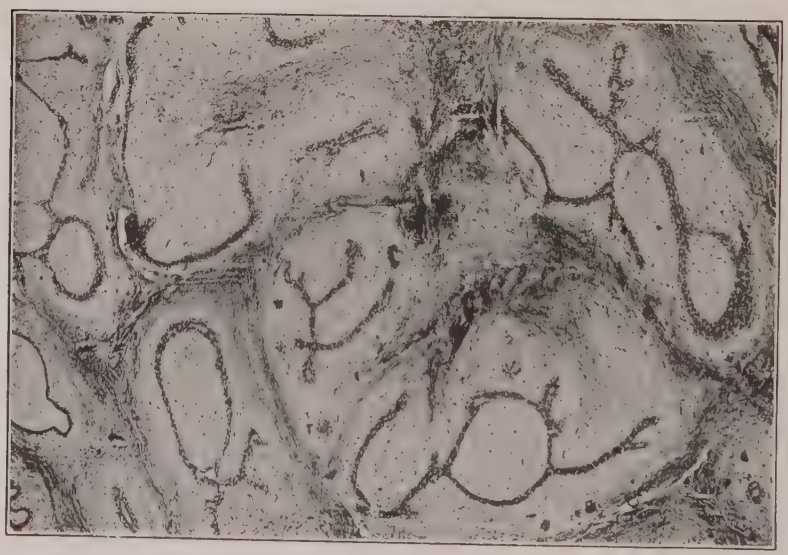


FIG. 260.—INTRACANALICULAR FIBROADENOMA OF BREAST.

adenoma is accordingly included by some writers[1] among the fibroepithelial tumors, in distinction to the carcinoma, where the epithelium forms the greater part of the neoplasm.

In still other respects does the adenoma imitate the organ in which it arises. There is considerable morphological resemblance between it

[1] *e.g.*, *Ribbert*, Geschwulstlehre, 2d ed., Bonn, 1914, p. 502.

and the normal architecture of the part, its alveoli and ducts usually having a lumen and a membrana propria. The physiological task of the organ is also undertaken, and a more or less characteristic secretion is produced, which often finds no outlet, since the glands may have no connection with the ducts of the organ in which they are situated.

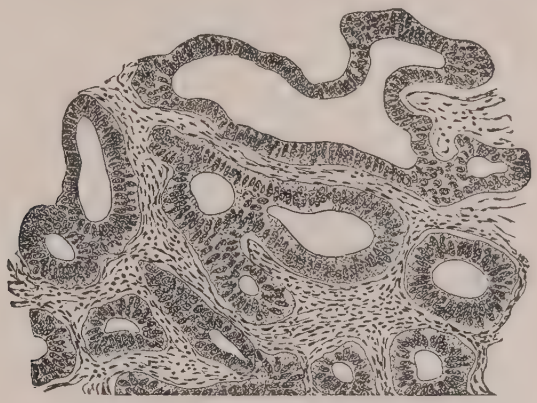


FIG. 261.—ADENOMA OF STOMACH.
A form of tumor which is on the border line of carcinoma and might be called adenocarcinoma.

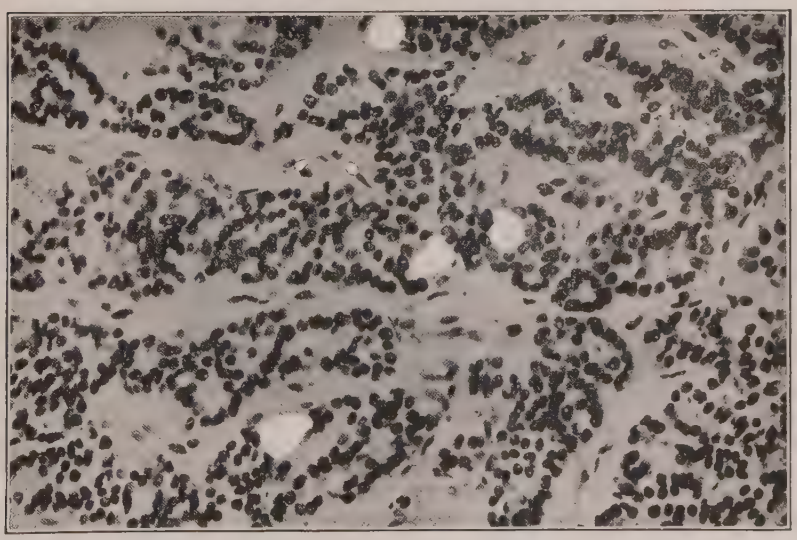


FIG. 262.—HYPERPLASIA OF THYROID TISSUE WITHOUT THE FORMATION OF COLLOID.
Often called fetal adenoma of thyroid.

Cystic dilatation is, therefore, a common event (*cystadenoma*). When papillæ grow into the cysts from their walls, a *papillary cystadenoma* is the outcome. An adenoma in which the proliferation of the connective tissue is more vigorous than usual is known as a *fibroadenoma;* this type is common in the breast, where it is called either *intracanalicular* (Fig. 260)

or *pericanalicular* fibroadenoma, according to whether the stroma compresses the glands in its growth or merely surrounds them. Myxomatous degeneration of the connective tissue of an adenoma sometimes occurs, and is particularly common in the intracanalicular fibroadenoma.

The concept adenoma is not yet so clear as might be wished. Thus, there is a condition in the breast (*Schimmelbusch's disease, maladie de Reclus*) which some authorities regard as a *chronic cystic mastitis* (König), others as a *senile parenchymatous hyperplasia*, and still others as *fibrocystadenoma*.[1]

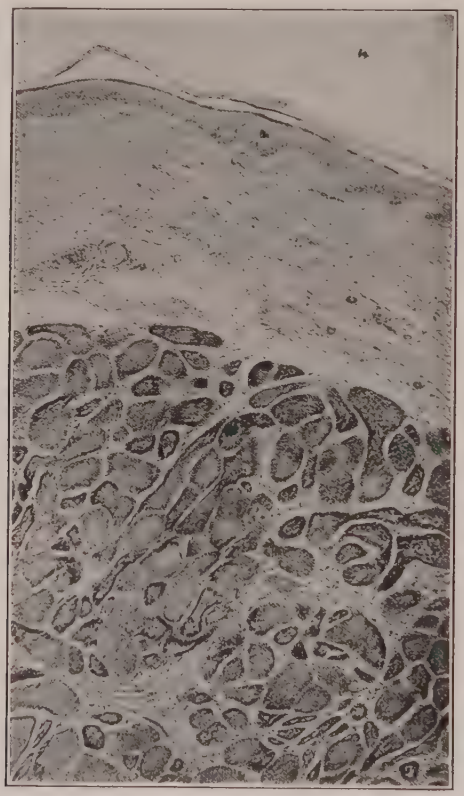


Fig. 263.—Sebaceous Adenoma from Skin of Forehead.

The old term *malignant adenoma* is falling more and more into disuse,[2] for it is becoming increasingly evident that in tumors which would previously have been described by this term the histological signs of malignancy are almost always to be discovered when they are carefully sought (Fig. 261).[3]

[1] For extensive descriptions of this condition, see *Berka*, Zieglers Beitr., 1912, liii, 284 (bibl.); *Greenough* and *Hartwell*, Jour. Med. Research, 1903, N. S. iv, 416 (bibl.).

[2] *v. Hansemann*, Virchows Arch., 1900, clxi, 453; for a discussion of the opposite side of the question see *Selberg*, ibid., 1900, clx, 552 (bibl.).

[3] See, for example, *Eggel*, Zieglers Beitr., 1901, xxx, 506.

Adenomata occur in the mamma, ovary, liver, kidney, adrenal, in the thyroid (Fig. 262), salivary, and lachrymal glands, and in the caruncle; in the mucous membrane of the nose, pharynx, stomach, and intestine,[1] and uterus, and occasionally in the sebaceous (Fig. 263) and sweat glands.[2]

Epithelial Tumors—Malignant.

CARCINOMA.

A carcinoma is a malignant neoplasm of epithelial origin. The normal arrangement characteristic of the cells from which the growth develops is abandoned, and such a tumor often consists chiefly of a chaotic mass of vigorously proliferating cells. Frequently, however, there is more or less imitation of the architecture of the organ involved, though this is hardly ever so complete as in the adenomata. The conditions among the epithelial new growths are similar to those obtaining in the connective-tissue series, and it is possible to build up a complete scale, beginning with the carcinoma which consists of a mere mass of cells; continuing with that which shows some approach to the normal structure; passing thence to the adenoma, where the architecture of the part is more or less faithfully copied; and ending, finally with the normal organ.

As with the connective-tissue neoplasms, also, the less differentiated carcinoma is apt to be the most malignant.

Carcinoma is a common disease, destroying at least 100,000 people annually in the United States alone.[3] Though most of these persons are in the *cancer age* (*i.e.*, have passed the age of thirty-five), cancer being ten times as frequent at seventy as at thirty,[4] the impression is far too common that carcinoma never occurs in young people. It does, and not so rarely either;[5] and having occurred, is much more malignant than in older patients.

But though cancer is most common in those over thirty-five, the rate of incidence does not seem to increase indefinitely with advancing years; on the contrary, the curve appears to reach its height at about 60 to 70 and then to decline,[6] at least in the case of some of the organs.[7] Additional evidence on this point is necessary, however, before any dogmatic statement can be made, for the large number of deaths among the aged certified in some such indefinite way as "senile debility," may cover a number of cases of cancer.

[1] *Versé*, Arb. a. d. path. Inst. z. Leipzig, 1908, i, 1.

[2] *Landsteiner*, Zieglers Beitr., 1906, xxxix, 316 (bibl.).

[3] *Hoffman*, The Mortality from Cancer throughout the World, Newark, 1915, p. vii.

Among other studies, with extensive bibliographies, are those of *Riechelmann*, Berl. klin. Wchnschr., 1902, xxxix, 728; and *Redlich*, Ztschr. f. Krebsforsch., 1907, v, 261.

[4] *Bashford* and *Murray*, Second Sci. Report, Imperial Cancer Research Fund, London, 1905, part 1, p. 33.

[5] *Roger Williams*, The Natural History of Cancer, New York, 1908, p. 327; *Brüning* and *Schwalbe*, Handb. d. allg. Path. d. Kindesalters, Wiesbaden, 1912, i, erste Abt., p. 420; *Lindemann*, Ztschr. f. Krebsforsch., 1909, vii, 682; *Warthin*, Arch. Int. Med., 1915, xv, 444.

[6] *Roger Williams*, The Natural History of Cancer, New York, 1908, p. 319; *Wolff*, Die Lehre d. Krebskrankh., Jena, 1913, Teil iii, erste Abt., p. 89.

[7] *Bashford*, Deutsch. med. Wchnschr., 1913, xxxix, 4.

When the curve of the incidence of carcinoma is compared with that of sarcoma,[1] it is found that both rise for a time as age advances and then fall; but whereas the decline in the case of the curve for carcinoma sets in at 60 to 70, that for sarcoma begins at about 50.

More cases of carcinoma occur in women than in men, but only because the breast and the genital tract are so commonly attacked in the female. When cancer in these localities is subtracted from the total, the disease is found to be somewhat more common in men. In both sexes the gastro-intestinal canal furnishes a large proportion of cases; thus, in the United States in 1914, 37.9 per cent. of deaths from cancer were brought about by cancer of the stomach and liver, and 15.6 per cent. by cancer of the female genital organs.[2]

Colored persons appear to be less susceptible to cancer than white.[3]

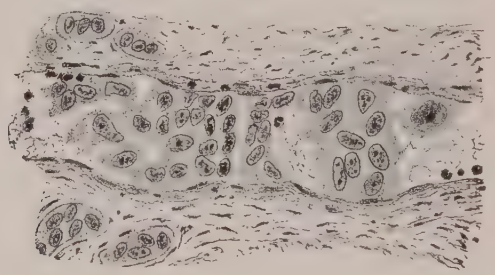


Fig. 264.—A Growth of Carcinoma Cells in a Lymph-vessel near a Tumor. Such cell masses are liable to be detached and carried along the vessel, forming metastases.

Multiple carcinomata (as well as multiple tumors of other varieties) occur in a small percentage of cases.[4]

Very rarely a carcinoma undergoes spontaneous cure.[5]

The carcinoma is prone to extension, usually by way of the lymphatics, through which the advancing tumor cells at the periphery make their way. Masses of these elements (Fig. 264) distend and grow along the lymph-channels (*lymphatic permeation*[6]) or detached cells or groups of cells may be swept along them to lodge in the adjoining lymph-nodes, where secondary nodules then develop (Fig. 265). On free surfaces the engorged lymphatics appear to the naked eye in form of a whitish elevated network; transverse sections of such channels are shown in Fig. 266 and 454.

Ulceration of a carcinoma permits the entrance of microorganisms, which set up more or less inflammation by which the regional lymph-

[1] *Weller*, Arch. Int. Med., 1915, xv, 518. See also other references on p. 427.

[2] Mortality from Cancer, etc., 1914, p. 15. Published by the Department of Commerce, Bureau of the Census, Sam. L. Rogers, Director of the Census. A similar preponderance is shown also by the Annual Reports of the Registrar-General of England.

[3] Mortality from Cancer, etc., 1914, p. 15. Published by the Department of Commerce, Bureau of the Census, Sam. L. Rogers, Director of the Census.

[4] *Warthin*, Jour. Am. Med. Assn., 1899, xxxii, 963 (bibl.); *v. Hansemann*, Ztschr. f. Krebsforsch., 1904, i, 483; *Redlich*, ibid., 1907, v, 285; *Goetze*, ibid., 1913, xiii, 281; *Gade*, Jour. Cancer Research, 1918, iii, 107; *Theilhaber* and *Edelberg*, Deutsch. Ztschr. f. Chir., 1912, cxvii, 457.

[5] *Theilhaber* and *Edelberg*, Ztschr. f. Krebsforsch., 1913, xiii, 461; *Rohdenburg*, Jour. Cancer Research, 1918, iii, 193 (bibl.).

[6] *Handley*, Cancer of the Breast, London, 1906, p. 56 ff.

nodes are usually involved. The *endothelial hyperplasia* (Fig. 310) which may thus be brought about may be mistaken for metastases, as the desquamated endothelium may appear to a careless observer to be groups of cancer cells.

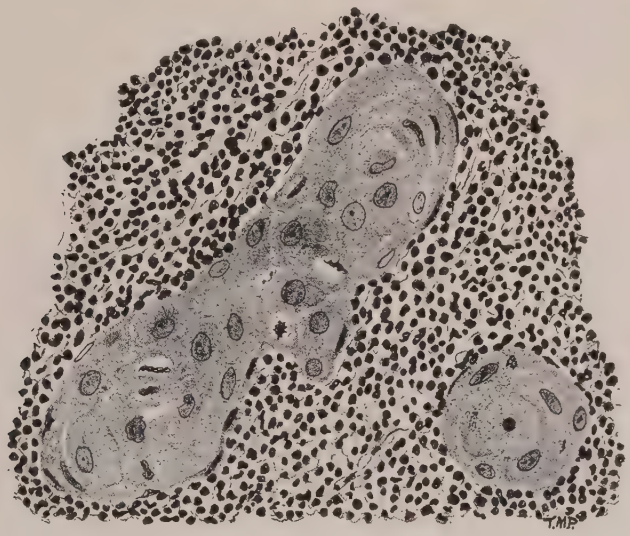


FIG. 265.—METASTATIC CARCINOMA (EPITHELIOMA) IN A LYMPH-NODE.
The primary tumor was in the vagina. The section shows at the right a small epithelial pearl.

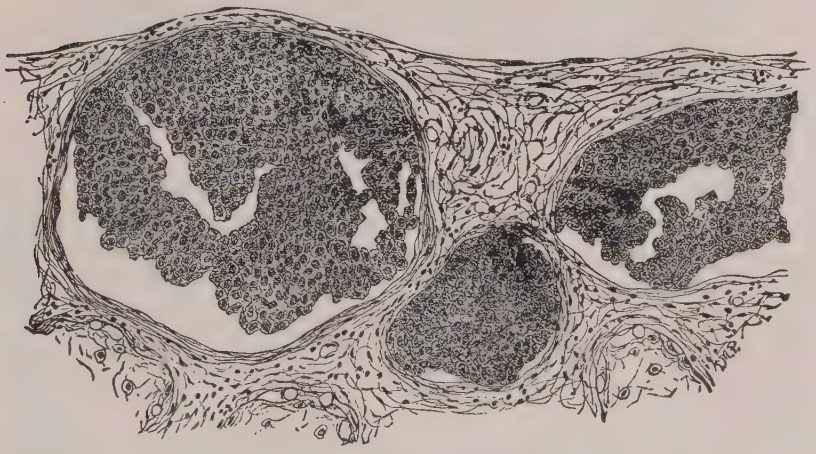


FIG. 266.—METASTATIC CARCINOMA IN LYMPH-VESSELS OF THE PLEURA.
The primary tumor was in the liver. The subpleural lymphatics are widely distended with the tumor-cell masses.

The parenchymal cells of a carcinoma are all descendants of the cell or cells in which the tumor started, and while they may closely resemble the type from which they are derived, they frequently differ considerably in appearance, owing to the vicissitudes of pressure, nutrition, functional

performance, etc. A great practical difficulty in the description, and, to beginners, in the recognition of the carcinomata and their varieties, lies in the great diversity of shape which their elements present. It should be always borne in mind that while the form of any cell does depend in part upon inherited growth tendencies, it is influenced also, and perhaps even in a greater degree, by the varying conditions of nutriment and pressure to which the cell is subjected during life. In the normal body these conditions conform to a certain standard, so that all cells of any one variety are approximately similar at a given stage of development. In tumors, however, the lawlessness of growth is such that many cells may be still immature, while even adult elements may depart widely from

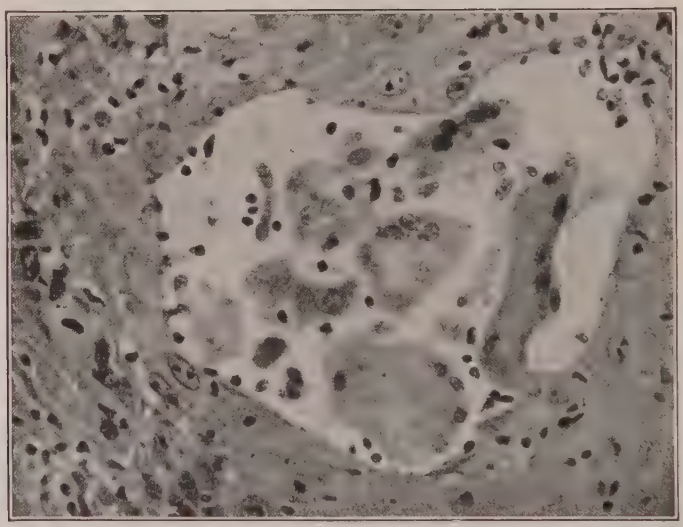


Fig. 267.—Epithelioma of the Cervix Uteri, Giant-cell Type.

their normal morphology. Thus, in a cylindrical-cell carcinoma, for example, there will be found many elements not yet fully developed and, like any other young cell, quite indifferent in form, as well as more mature elements which have never assumed the cylindrical shape.

Another source of confusion is introduced by inflammatory processes, which may give rise to young connective-tissue cells that are not to be distinguished individually from atypical epithelium.

Finally, carcinomata growing in loose tissue like a granulating cervix uteri, are particularly apt to contain cells of widely varying size and outline, owing to the absence of pressure. Even giant[1] cells may be found (Fig. 267).

Thus there is no morphologically typical *cancer cell*, as there was formerly supposed to be. Some are characteristic of their site of origin and some not; and while the more characteristic may resemble normal

[1] *Delamare* and *Lecène*, Arch. d. méd. expér., 1906, xviii, 102.

epithelium, the atypical may look like young connective-tissue cells or even like lymphocytes. It is from the topography and situation of the growth, therefore, together with the general character of its cells, that its nature must be determined.

Mitotic figures (Fig. 268) are usually more abundant in carcinomata and other malignant growths than in benign tumors and inflammatory processes, and such evidences of rapid proliferation can hardly be thrown out of court in determining the nature of a doubtful lesion. On the other hand, the rule is to be used with some caution. It would perhaps be unwise to attempt to measure the degree of malignancy by the number of mitotic figures,[1] for only a small portion of any neoplasm is examined by the pathologist in most cases, and there is no question that different parts of a tumor may at the same time proliferate at different rates. Close observation of the growth rate of tumors so situated that their dimensions can be accurately determined, shows, finally, that periods

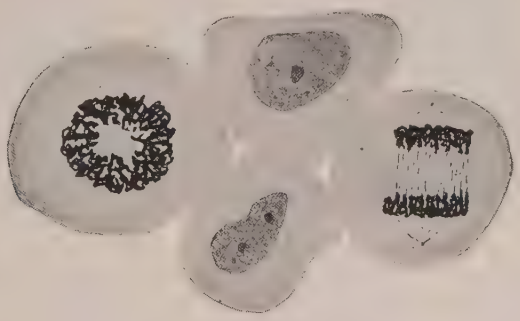


FIG. 268.—MITOSES IN CARCINOMA

of rapid increase alternate with stationary or even recessive phases. This fact, by the way, has often led to serious error in estimations of the supposed therapeutic effects of so-called cancer cures.

Carcinomata are liable to fatty, gelatinous, mucous, and amyloid degeneration, and are especially prone to ulceration (Fig. 269), hemorrhage, and inflammation (Fig. 270). They may become partially calcified and are not infrequently combined with other forms of tissue in the mixed tumors.

When carcinomata, or other primary or secondary malignant growths, encroach in their proliferation upon adjacent tissues, they bring about more or less destruction, either by pressure atrophy or by lysis. It frequently occurs that their cells are apposed to, or even infiltrate, structures similar to those in which the tumor originates, so that one may see malignant and non-malignant tissue growing side by side and presenting an almost identical appearance.[2] The cells adjacent to the neoplasm may also show evidence of proliferation in mitotic figures. These two features, contiguity and mitosis, have led many observers[3] to the con-

[1] *McConnell*, Jour. Am. Med. Assn., 1908, li, 910.
[2] *Rous*, Jour. Exper. Med., 1911, xiii, 239.
[3] *e.g.*, *Hauser*, Zieglers Beitr., 1897, xxii, 587.

FIG. 269.—CARCINOMA OF HAND.
This tumor is of the epitheliomatous type and presents a large, rough, ulcerated surface.

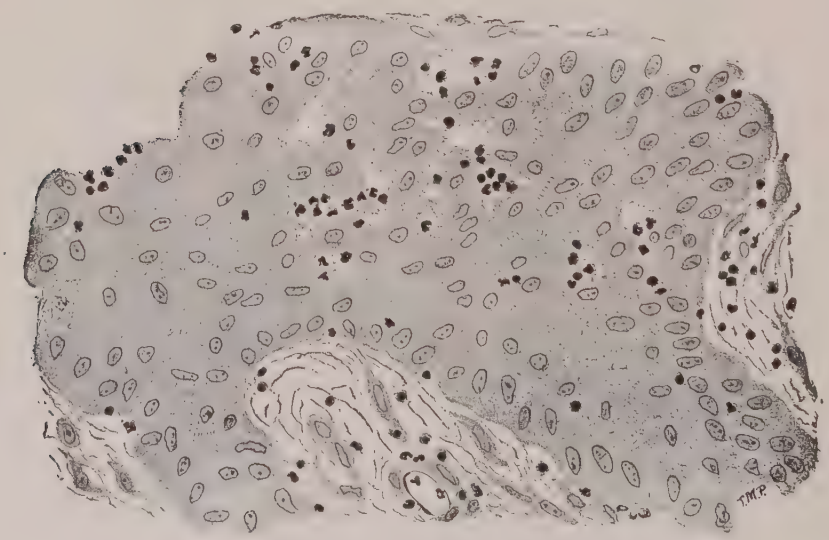


FIG. 270.—EXUDATIVE INFLAMMATION IN CARCINOMA.
Showing leucocytes in the stroma and in the epithelium. The epithelium is disintegrating, and in the small region shown in the cut the leucocytes are apparently acting as phagocytes in the softening and removal of the disintegrating epithelium.

clusion that the tissue adjoining a growing tumor may assume exalted powers of proliferation and share in the growth of the neoplasm, of which it may frequently become a part. But this view is erroneous, and the student of oncology should constantly remember that the characteristic cells of a new growth are the direct descendants of these elements in which it started, and that a neoplasm grows only by the proliferation of its own cells. It does not spread by successive waves of "cancerous degeneration."

Forms of Carcinoma

The cells of certain carcinomata of the skin and mucous membranes, imitating the type of epithelium from which they arise, are apt to become flattened or squamous as they grow older; these tumors are called *squamous-* or *flat-cell* carcinomata, or simply *epitheliomata.* In another class of growths, such as frequently attack the gastrointestinal canal and the uterus, the cells are more or less cylindrical in shape, forming a palisade-like lining to the irregular alveoli; such neoplasms are called *cylindrical-cell* carcinomata. There is a third and very common form often derived from cuboidal epithelium, in which the cells have no constant characteristic shape, but vary as much as do elements of the various glands throughout the body. Such tumors are sometimes called *carcinoma simplex.* A carcinoma which contains an abundant supply of blood-vessels is called a *carcinoma telangiectoides.*

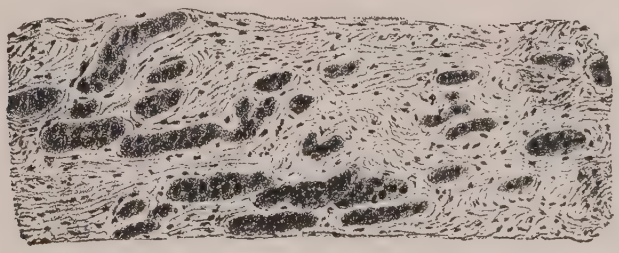


Fig. 271.—Fibrocarcinoma or Carcinoma Durum (Scirrhous Carcinoma).

Perhaps somewhat more useful than this purely morphological classification is that which divides carcinomata, according to the site of their origin, into *epidermal* and *glandular* carcinomata.

A third method of subdivision is based upon the quantitative relations between parenchyma and stroma. A carcinoma consisting almost entirely of parenchyma is called a *medullary* or *encephaloid* carcinoma, or *carcinoma molle* (Fig. 252); one with approximately equal amounts of parenchyma and stroma is a *carcinoma simplex;* while one in which the stroma distinctly preponderates is known as a *scirrhous* carcinoma or simply as a *scirrhus* (Fig. 271). The first type, as a rule, is perhaps even more malignant than the last. While in the scirrhous variety the stroma may become so dense as nearly to obliterate the epithelium, it is very

doubtful if any considerable area ever undergoes spontaneous cure in this way.

In addition to the varieties already mentioned there are several others, which depend for their characteristics on various degenerations and metamorphoses, such as *gelatinous carcinoma* (Fig. 272), *melanocarcinoma* (page 477), etc.

It will be most advantageous to give a brief description of the various kinds one after another, with the understanding that they are not specific forms, but simply varieties which it is convenient to recognize for clinical and anatomical purposes; and that few tumors, in any case, offer an entirely pure example of any one type.

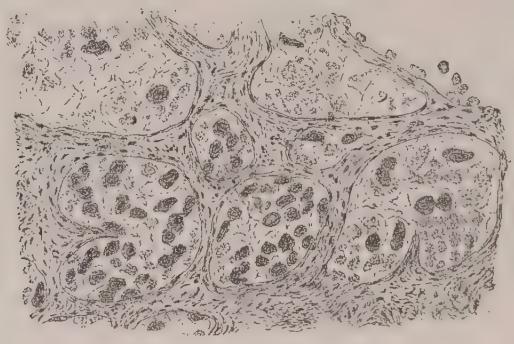


Fig. 272.—Carcinoma Gelatinosum—Colloid Cancer.
From a tumor of the stomach.

Epithelioma (*Cancroid*).—New growths of this class occur in the skin, and in the mucous membranes which are covered with squamous epithelium, their cells presenting all the various forms which normally exist in these parts.

In order to understand their manifold appearance under the microscope, the structure and functional characters of the normal skin should be borne in mind. The epithelium rests upon connective tissue, the corium or true skin, from which its nutriment is derived. The cells of its deeper layers, the rete Malpighii, are cuboidal and polyhedral; over these lie several layers of more or less flattened elements, while upon the surface the cells are scaly and keratinized. The typical epithelial cell is the prickle cell or spine cell, joined to its neighbors by intercellular bridges.

The various forms of cell in squamous epithelium represent regular phases of development, as the younger and larger cells underneath are pressed outward to flatten and finally desquamate. In epitheliomata, the cells have in a measure the same life history, though as they are no longer growing on a flat surface, but in inclosed spaces, they become packed into masses where the older elements are forced toward the centers. So there is formed at length a number of groups of concentrically arranged elements (*epithelial pearls*, Fig. 273). It is important to remember, however, that these are not characteristic of the epitheliomata, for any con-

dition which involves the growth of squamous epithelium into limited spaces may result in their formation. They are of value only because they may clear up the origin of a doubtful tumor, for while they do not in any sense prove that the *lesion* in which they are found is a true neo-

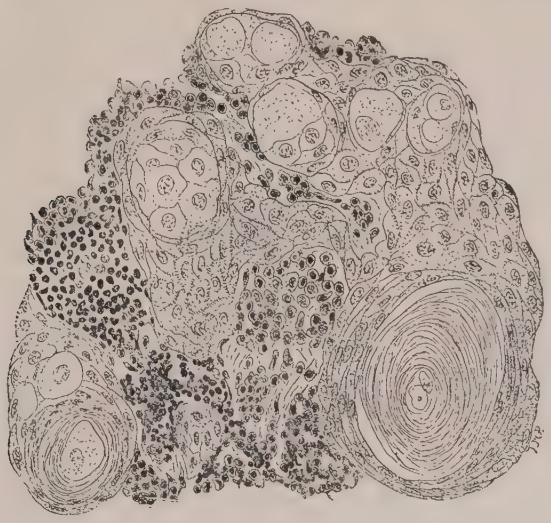


FIG. 273.—EPITHELIOMA OF AXILLARY LYMPH-NODE.

This metastatic tumor was secondary to a large epithelioma of the back of the hand. The small cells with darker nuclei are the cells of the lymph-node. It shows the epithelial pearls in various stages of formation.

FIG. 274.—EPITHELIOMA OF SKIN.

Showing reticular masses of epithelial cells with fibrous stroma.

plasm, they do suggest that any *tumor* in which they are discovered has originated in surface epithelium. They suggest this, but do not prove it, for in certain rather rare cases other neoplasms (of the mamma, the body of the uterus, or the gall-bladder, for example) may contain

squamous epithelium;[1] whether this is the outcome of metaplasia, or of the presence of embryonal cell rests, is not known. The demonstration of prickle cells in a growth is of equal value.

The alveoli of an epithelioma may be large or small, and separated by abundant or scanty stroma; except in incipient tumors they form a reticular mass (Fig. 274) which infiltrates the tissues more and more deeply; at the same time the tumor may project above the surface in the form of a papillary growth. Ulceration (Fig. 269) is common and the surrounding skin is apt to become thickened (Fig. 275). It is this thickening of the skin and its elevation by the burrowing tumor that confers

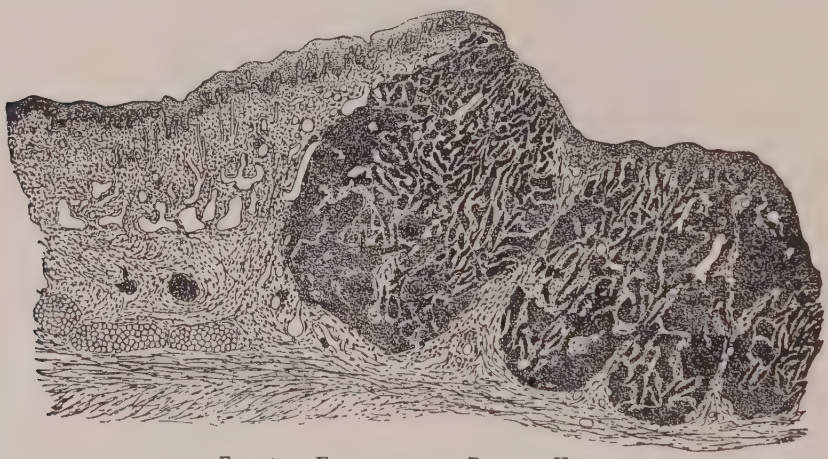


FIG. 275.—EPITHELIOMA OF BACK OF HAND.

The flat tumor occupied nearly the entire back of the hand, and was ulcerating at the surface. The figure shows the edge of the tumor and a portion of the ulcer. The papillæ of the skin over the edge of the growth are hypertrophied, and the tissue about is infiltrated with small spheroidal cells. Fig. 273 shows a section from a metastatic tumor of the axillary lymph-node in this case. This tumor presented the gross appearance shown in the photographic reproduction in Fig. 269.

upon ulcerating epitheliomata, especially those of the mucous membranes the characteristic pearly overhanging edge that distinguishes them from tuberculous and syphilitic ulcers.

Epitheliomata are apt to occur at a mucocutaneous junction (lips, nostrils, eyelids, labia, and glans penis), and are frequent also in the mouth, esophagus, vagina, and the cervix uteri; they sometimes develop in nævi.

Under the name **basal-cell carcinoma** a group of tumors (Fig. 276, and 277) has been described,[2] which differ both clinically and histologically from other carcinomata. These do not arise at a mucocutaneous junction, but at certain characteristic sites like the temple, forehead, cheek, and nose; as a general rule it may be said that a carcinoma of the face above the line of the upper lip will prove to be a basal-cell carcinoma; below that level, a squamous-cell carcinoma. The basal-cell carcinoma occurs in old people in the form of an ulcer (*rodent ulcer*,

[1] *Herxheimer*, Zieglers Beitr., 1907, xli, 348 (bibl.); *Lubarsch*, Verhandl. d. deutsch. path. Gesellsch. 1906, x, 198, 208.

[2] *Krompecher*, Der Bazalzellenkrebs, Jena, 1903; Zieglers Beitr., 1905, xliv, 51 and 88.

Jacob's ulcer), which often persists for years and almost never metastasizes. It is, in fact, the most benign of all the malignant neoplasms and one which can readily be cured by excision or by the application of carbon dioxide snow, *x*-ray, or radium. Histologically the growth is

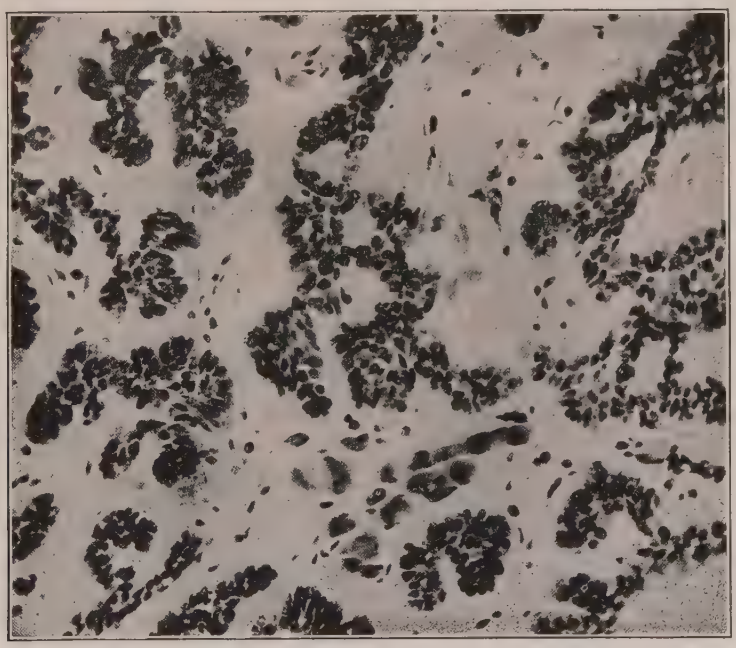


FIG. 276.—BASAL-CELL CARCINOMA; METASTASIS IN THE MUSCLE OF ABDOMINAL WALL
The stroma is extremely edematous and contains very few cells.

composed of cells resembling those of the basal layer of the skin in their lack of differentiation; that is, of small oval or spindle-shaped elements with deeply staining nuclei and cell bodies, no spinous process, and no tendency toward keratinization; a gyrate or glandular arrangement is

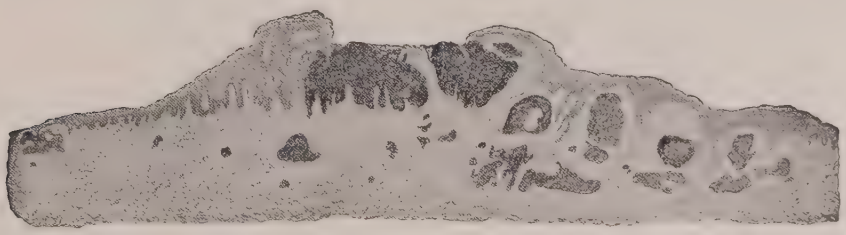


FIG. 277.—SMALL SUPERFICIAL BASAL-CELL CARCINOMA OF THE FACE.

sometimes evident. The rather uncommon tumors of this class in which keratin is present (Fig. 278) are regarded as transition forms between the basal-cell and the squamous-cell carcinomata. Though the most

characteristic site of the basal-cell carcinoma is the face, these growths may arise from any squamous epithelial surface or from glands opening upon such a surface.

Not all authorities agree with the ideas of Krompecher, briefly reproduced in the preceding paragraph. Thus, since its cells resemble

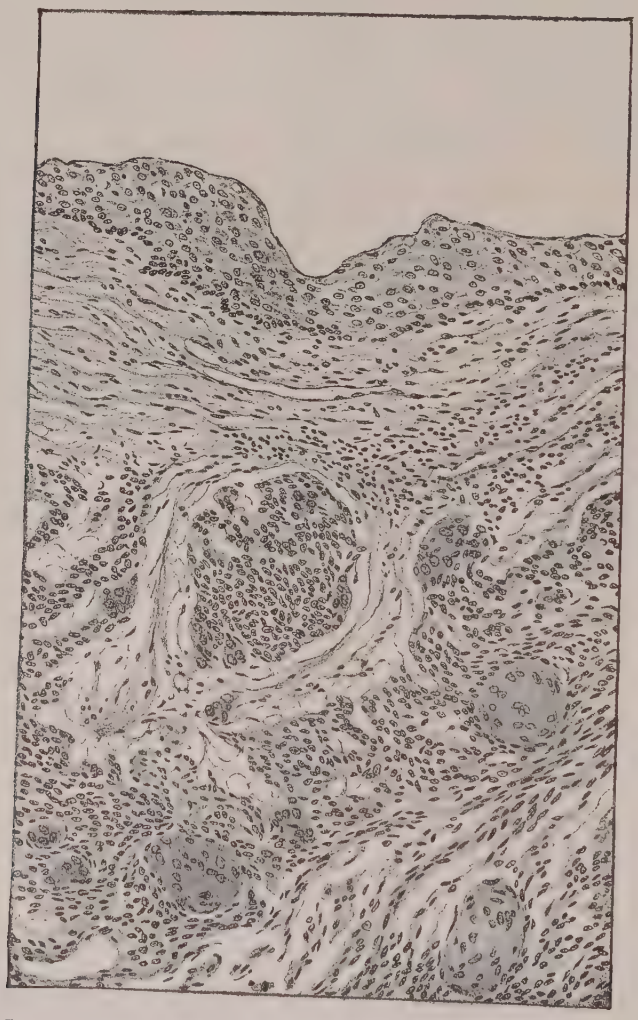


FIG. 278.—BASAL-CELL CARCINOMA CONTAINING KERATINIZED AREAS. Several of these areas can be seen in the lower right-hand corner of the cut.

those of hair follicles and sebaceous glands, the basal-cell carcinoma has been said to arise in these structures and has been called *trichocarcinoma* (Fig. 279) or *adenogenous* carcinoma;[1] and since the growth often has no connection with the surface epithelium, it has been asserted that the

[1] *Ribbert*, Das Karzinom des Menschen, Bonn, 1911, p. 51.

basal-cell carcinoma originates from epithelial remnants in the true skin, and it has on this account been called *corium* carcinoma.[1]

Differential Diagnosis.—The spindle shape of their cells gives these growths a certain superficial resemblance to the sarcoma, from which they can usually be distinguished, however, by the possession of such characteristics as: the uniform size and shape of the cell bodies and nuclei, the affinity of both for basic dyes, a gyrate or glandular arrangement, a paucity of mitoses, and, finally, a history of comparative benignancy.

Fig. 279.—Trichocarcinoma from Cheek.

The mixed tumors of salivary glands previously referred to (page 453) are regarded by some observers as basal-cell carcinomata.[2]

Cylindrical-cell Carcinomata.—These tumors, sometimes distinguished with difficulty from the adenoma (Fig. 261), occur in the stomach, intestine, and uterus. The cells are loosely or closely packed in larger or smaller alveoli which are separated from one another by a stroma more or less dense. These growths merge imperceptibly into the next class.

Carcinoma Simplex.—Neoplasms of this variety, by far the most frequent of the carcinomata of internal parts, are characterized by irregular, anastomosing alveoli, sometimes solid, sometimes containing spaces which recall the lumina of glands, and inclosed by a more or less abundant fibrillar stroma approximating the parenchyma in amount. The epithelial cells may or may not resemble the epithelium of the gland in which the growth originates; they have no uniform shape, but may be

[1] *Borrmann*, Ztschr. f. Krebsforsch., 1904, ii, 1; 1906, iv, 91.
[2] *Krompecher*, Zieglers Beitr., 1908, xliv, 51.

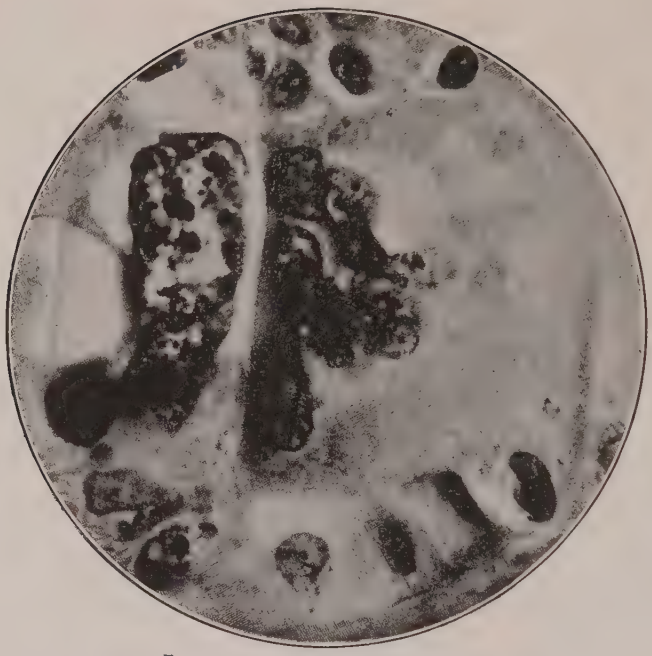


FIG. 280.—CARCINOMA OF MAMMA.
Showing fused cells producing appearance resembling syncytium.

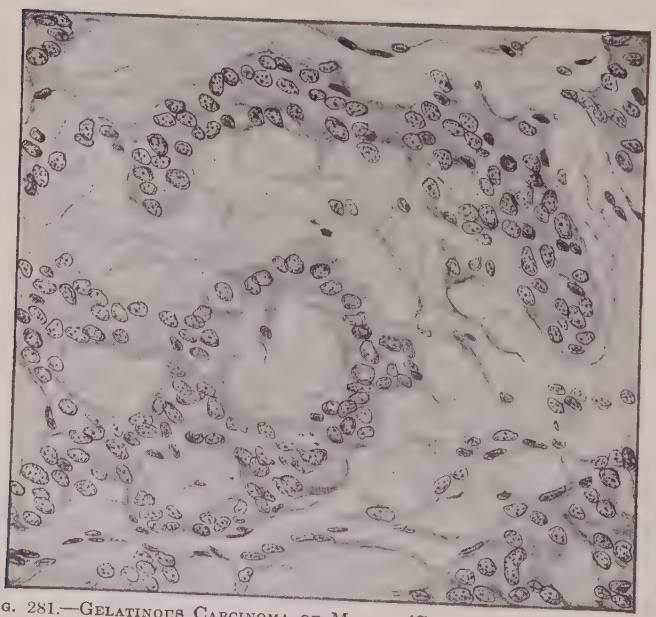


FIG. 281.—GELATINOUS CARCINOMA OF MAMMA (CARCINOMA MYXOMATODES.)
Of ten years' duration without metastasis.

cuboidal, polyhedral, spheroidal, or fusiform, and are often so merged that they resemble a nucleated mass of cytoplasm (a *syncytium*) rather than an aggregate of individual cells (Fig. 280).

Gelatinous Carcinoma.—In the cells of certain carcinomata, especially of the gastrointestinal canal, a translucent, gelatinous material (*mucin*) may collect, but whether it appears as the result of secretory activity or of degeneration is not known. Such tumors have been called *colloid cancers*, though the material which characterizes them is not true colloid. In some cases the amount of mucin is only moderate, the cells containing more or less of it in the form of translucent droplets; but in others large areas of the parenchyma are partially or entirely destroyed and replaced by mucin (Fig. 272). Sometimes only part of a tumor undergoes gelatinous transformation.

The stroma of a carcinoma may be the seat of myxomatous degeneration (*carcinoma myxomatodes*,[1] Fig. 281) like that seen in sarcomata or in the connective-tissue constituent of fibroadenomata of the breast.

Melanocarcinoma.—Tumors of this sort, which are distinctly rare, are characterized by the presence of variable quantities of black or brown pigment granules in the parenchyma (Plate II, Fig. 1). They are usually soft and malignant, and occur most frequently in the skin (see page 443). One has been recorded which contained keratin, establishing its epithelial nature.[2]

Bibliography of Tumors.

An extensive and important work on tumors, containing a vast store of information, is *Rudolf Virchow's* Die krankhaften Geschwülste, Berlin, 1863; it is old and is not complete, but is still invaluable as a work of reference. An admirable review of the whole subject has been prepared by *Wolff:* Die Lehre von der Krebskrankheit, Jena, 1914. A very useful bibliography will be found in *Ziegler's* Lehrbuch der allgemeinen Pathologie, Band I, Jena, 1905. An important résumé on the malignant tumors in childhood, by *Stern*, may be found in the Deutsch. med. Wchnschr., 1892, p. 494, and another, by *Merkel*, in Brüning and Schwalbe's Handbuch der allgemeinen Pathologie des Kindesalters, Wiesbaden, 1912. Current additions to the subject may be found in the files of Lubarsch and Ostertag's Ergebnisse der allgemeinen Pathologie; see particularly *Lubarsch*, 1895, i², 289; and 1899, vi, 952; *Aschoff*, 1898, v, 73; *Fisher* and others, 1904–05, x, 643; and *Herxheimer* and *Reinke*, 1913, xvi², 1; *Borst's* Die Lehre von den Geschwülsten, Wiesbaden, 1902, is a valuable work with many excellent illustrations and a bibliography, as is also *Ribbert's* Geschwülstlehre, 2d ed., Bonn, 1914. Other oncological monographs are *Ribbert's* Das Karzinom des Menschen, Bonn, 1911; *Williams'* Natural History of Cancer, New York, 1908; *Behla's* Carcinomlitteratur, Berlin, 1901; *Contamin's* Cancer expérimentale, Paris, 1910;

[1] For a discussion of this and the preceding type of carcinoma, see *Ribbert*, Das Karzinom des Menschen, Bonn, 1911.

[2] *Beckey*, Frankfurt. Ztschr. f. Path., 1915, xvii, 364 (bibl.).

Menetrier's Cancer, Paris, 1909; *Thomas's* Cancer, Paris, 1910; *Roffo's* Cancer experimental, Buenos Aires, 1914; *Bland-Sutton's* Tumors Innocent and Malignant, New York, 1917; *v. Hansemann's* Atlas der bösartigen Geschwülste, Berlin, 1910; *Cullen's* Cancer of the Uterus, New York, 1900; *White's* Pathology of Growth: Tumours, London, 1913; *Kettle's* Pathology of Tumours, New York, 1916; *Borrmann's* Wachstum des Magencarcinoms, Jena, 1901; *Adler's* Primary Malignant Growths of the Lungs and Bronchi, New York, 1912; *Bashford, Murray,* and others in the Scientific Reports of the Imperial Cancer Research Fund, London, 1908–12; Studies in Cancer and Allied Subjects, from the Crocker Fund, Columbia University, New York, 1912–13; *Woglom's* Study of Experimental Cancer, New York, 1913; *Cornil's* Tumeurs du sein, Paris, 1908; *Henke's* Praktische Anleitung zur Untersuchung von Geschwülsten, Jena, 1906; *Clunet's* Recherches expérimentales sur les tumeurs malignes, Paris, 1910; Fölger, A. F., Geschwülste bei Tieren, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1917, xviii², 372 (bibl.); Lockyer, C., Fibroids and Allied Tumors, London, 1918; Kelly, H., and Cullen, T. S., Myomata of the Uterus, Philadelphia, 1909; Cullen, T. S., Diseases of the Umbilicus, Philadelphia, 1916; Adenomyoma of the Uterus, Philadelphia, 1903.

CHAPTER XII.

GENERAL DISEASES.

In the so-called general diseases, various parts of the body are structurally or functionally involved, but there is usually a primary lesion in some special organ. The grouping of certain diseases under this heading is rather for convenience than because these diseases are fundamentally different in their relations to the body as a whole from many others, such as infections, intoxications, etc. Fever, which is so often one of the manifestations of toxemia, has been grouped with the general diseases, because in some respects it presents important analogies with them.

CACHEXIA STRUMIPRIVA—MYXEDEMA.

The thyroid is one of the ductless glands which furnishes internal secretions essential to normal metabolism in the body.

Removal or destructive lesions of this gland, both in man and the lower animals,[1] may be followed by serious and fatal disease characterized as *cachexia strumipriva*. In man the more common manifestation of this disease is called *myxedema*.[2] It occurs most frequently in middle-aged women.

The skin of the face is apt to be swollen and waxy, giving a peculiar and rather characteristic appearance to the features (Fig. 282). The skin of the body is apt to be dry and rough, and the hair may fall out. Perspiration is, as a rule, diminished. The general body metabolism is diminished while glucose tolerance is increased. Glycosuria however, may be found. The mental condition is dull, and loss of memory and insanity may occur. Bodily movement and speech are apt to be impaired. The fat tissues may be atrophic, and the subcutaneous tissue has been shown in some, though not all, of the cases to contain an unusual amount of mucin. In some cases the fibers of the upper layers of the corium are crowded apart by fluid.

The most marked and constant lesion in this disease is an atrophic condition of the thyroid gland. The parenchyma of the gland is more or less completely replaced by fibrillar connective tissue, and by newformed reticular tissue resembling the lymphatic tissue of the lymphnodes. The general appearance of the atrophied thyroid gland is shown in Fig. 284.

In addition to the lesion of the thyroid there are apt to be chronic endarteritis and chronic diffuse nephritis. In some cases there is an accumulation of small spheroidal cells about the smaller blood-vessels in various parts of the body, and also petechial hemorrhages.

[1] For an extensive critical and experimental study of this subject, see *Cunningham, R. H.*, Experimental Thyroidism, Jour. Exper. Med., 1898, iii, 147 (bibl.). For a study of the transplantation of the thyroid, see *Payr, E.*, Arch. f. klin. Chir. (Langenbeck), 1906, lxxx, 730.

[2] For bone lesions in this condition, see page 1064.

If the thyroid is completely removed in young animals there is deficient development of the osseous system, while in man the frequent association of cretinism with goiter or other thyroid lesions indicates in another way the close relationship between the thyroid and cell metabolism.[1]

Cretinism is a congenital condition in which development is retarded and faulty.[2] An adult in years is often infantile or childish in stature and mental capacity, ill formed and uncouth (Fig. 283).

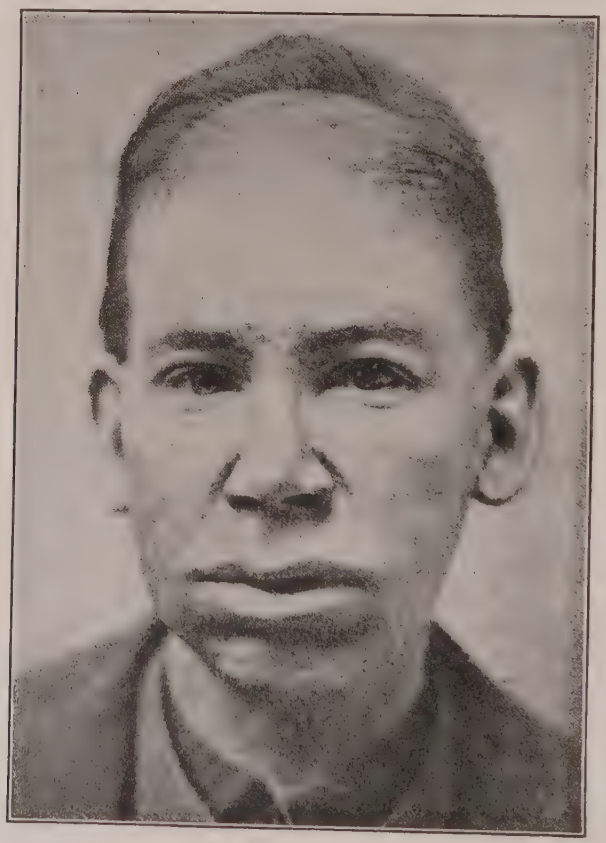


FIG. 282.—MYXEDEMA.
Showing "puffy" skin of face and falling of the hair—case of Dr. Henry Hun.

The nature of the substances composing the internal secretions of the thyroid is little understood, but the wonderful therapeutic effects of the administration in cases of myxedema and in cretins of the extract of the gland in which they are deficient, make clear their great importance. Whether directly toxic substances are formed in the thyroid or

[1] Consult *Osler*, Sporadic Cretinism in America, Trans. Cong. Am. Phys. and Surg., 1897, iv, 169.
[2] For bone lesions, see page 1064.

FIG. 283.—A CRETIN.
About twenty years of age.

not, it seems proper to consider the cachexia strumipriva as due directly or indirectly to autointoxication.

EXOPHTHALMIC GOITER. (Basedow's Disease, Graves' Disease.)

The lesions of this disease are unilateral or bilateral enlargement of the thyroid gland and protrusion of the eyeballs—*exophthalmos*. Associated with these is hyperplasia of the lymphatic system, which is especially marked in the thymus, spleen, and lymph-nodes. Correlated with this lymphoid overgrowth is a relative or absolute increase in the lymphoid elements of the blood, and, in addition, there are certain characteristic disturbances, among them rapid heart action—*tachycardia*—and muscular tremor. The pathological changes found in the thyroid are extremely complex.

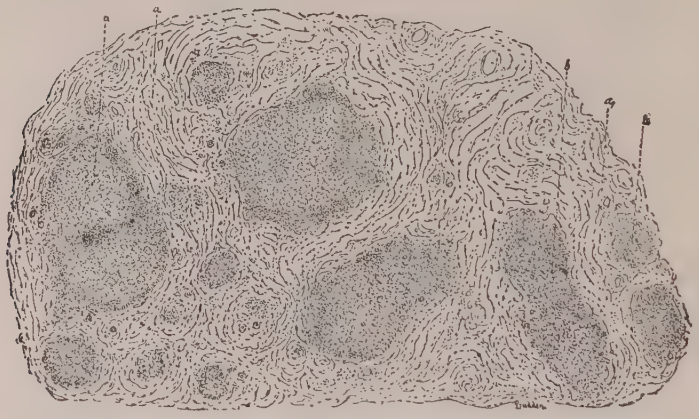
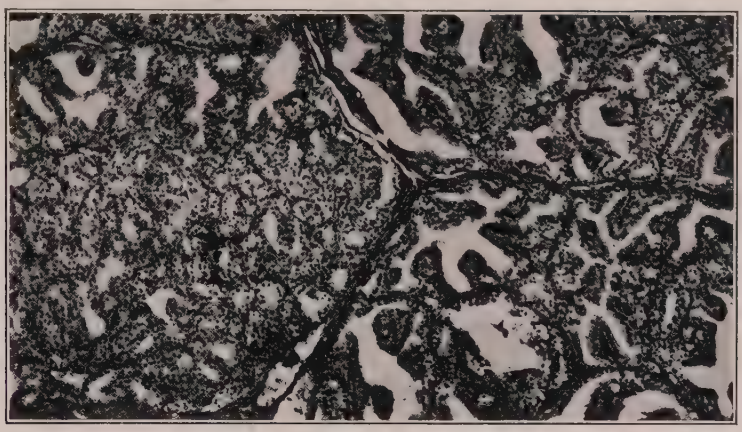


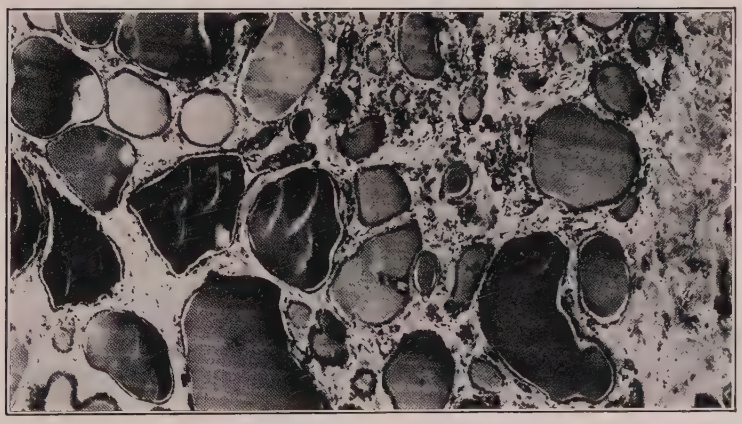
FIG. 284.—SECTION OF THE ATROPHIED THYROID GLAND IN MYXEDEMA.
a, Interstitial tissue; *b*, atrophied lobules with small spheroidal-cell or lymphatic tissue in their peripheries.

In the patients more active clinically, the gland is of a reddish color, of firm consistency, and symmetrically enlarged. It is encased in a thin fascial sheath containing large blood vessels. Lobulation is visible, and on section the surface is granular, and if the case is advanced, no colloid vesicles can be seen. A thin slice is not translucent. In the typical cases the lesions correspond with those shown in Plate III, No. 1. Microscopically there is marked hyperplasia of the gland structures, the epithelium is high and columnar, mitochondria are abundant, the numbers being in proportion to the cell activity.[1] As the hyperplastic process continues, the epithelial elements increase in number and because of this overgrowth form papillary projections into and even completely obliterate the lumen of the vesicles. In other types numerous small vesicles, without change in the height of the epithelium, may be formed. The colloid loses its affinity for eosin and slowly decreases in amount

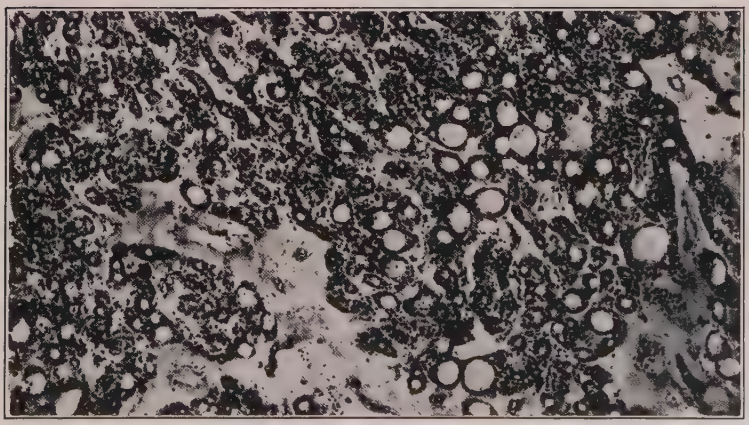
[1] *Seecoff, D. P.*, Am. Jour. Path., 1925, i, 295.



EXOPHTHALMIC GOITER × 75



COLLOID GOITER × 75



FETAL ADENOMA OF THYROID × 57

until it is entirely absent in long standing cases. It begins to disappear near the periphery of the gland where vacuoles form (Fig. 286). In addition to the changes in the gland substance the connective tissues throughout the thyroid are increased in amount, lymphoid foci appear throughout the gland, and the vascular channels enlarge. Various degenerative changes may be found in long standing examples. In the late cases exhaustion atrophy may result, evidenced by extensive small cell infiltration, fibrosis of the stroma and islands of hyperplastic cells scattered throughout, giving the histological picture of myxedema.

If during the course of the disease iodine is administered, extensive changes rapidly occur. The gland shrinks, is much softer, the blood

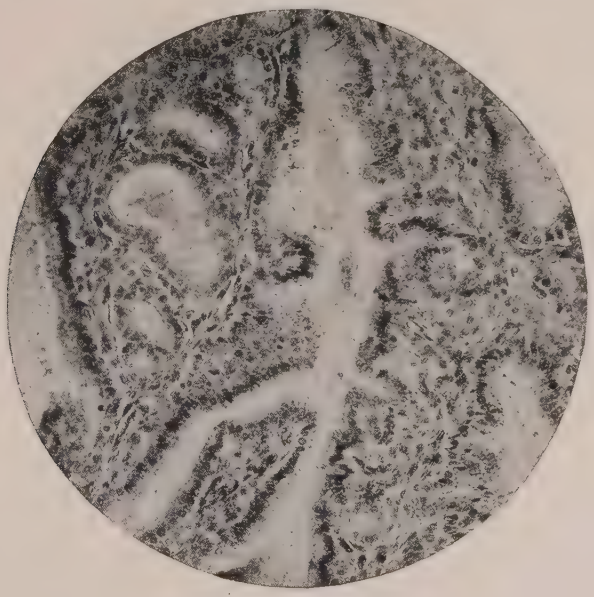


Fig. 285.—Exophthalmic Goiter before Iodine. Very Little Colloid. 0.3 Mgm. Iodine per Gram of Dried Tissue. × 150.

vessels are smaller, a fresh section is a pale brown color, colloid vesicles can easily be made out, and a thin slice is very translucent. Microscopically the hyperplastic changes show a state of regression toward a normal or colloid condition. The epithelium changes from columnar to flat, the papillary projections disappear and an increased amount of colloid makes its appearance. Lymphocytic foci remain as well as numerous connective tissue scars. The amount of change found depends upon the original severity of the disease and the amount and duration of the administration of iodine. While a very hyperplastic gland shows but little iodine on analysis, after treatment and regression the quantity is much increased (Fig. 286).

The above is a description of a classical exophthalmic goiter, but the same syndrome may occur and the glands show the lesions of a colloid goiter, with large alveoli filled with normal colloid and lymphoid tissue

in the stroma. Adenomata either of the fetal or of tumor type may be present. Finally the changes found may be highly complex in a patient suffering from clinical exophthalmic goiter when the disease develops on an old colloid goiter, the hyperplastic structures being commingled with cysts, hemorrhagic areas, calcification and nodules of adenoma. The heart usually shows a considerable hypertrophy of the left ventricle which is due to the extra labor falling on that portion of the organ owing to the extreme rapidity of the pulse. Some of the symptoms of myxedema are frequently shown by patients suffering from exophthalmic goiter

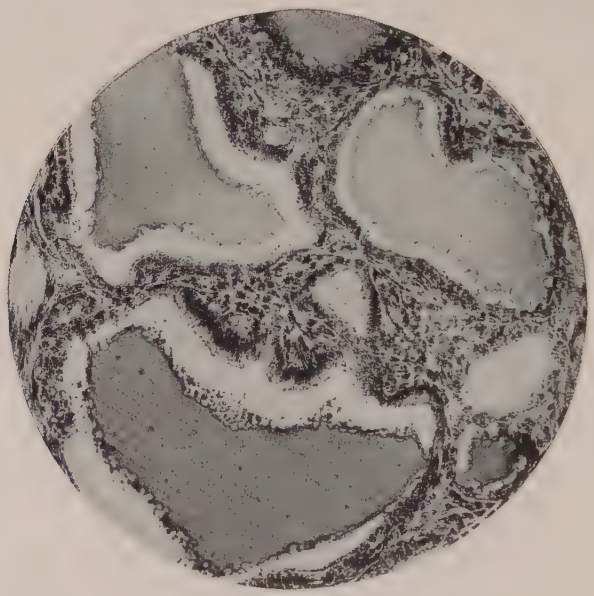


Fig. 286.—Exophthalmic Goiter after Iodine. Abundant Colloid. 1.5 Mgm. Iodine per Gram of Dried Tissue. × 150.

and the terminal stage of excessive radiation treatment may be an atrophy of the glandular structure with the ultimate production of myxedema.

Some degree of ventricular hypertrophy exists in advanced exophthalmic disease. The muscle is pale, soft and there is often a moderate degree of dilatation. The muscle fibres are swollen and fatty. Areas of connective tissue fibrosis are often present. These may possibly be due to the muscle necrosis with fibrosis which has been found after giving thyroxin[1] and in fatal cases of goiter.[2]

Four theories are current in explanation of this condition. The first is that it is due to *hyperthyreosis* or excessive secretion of the thyroid gland. This is based upon the fact that overdoses of thyroid extract produce some of the symptoms of exophthalmic goiter and that removal of a portion of the gland or ligature of some of its vessels is often beneficial

[1] *Goodpasture*, Jour. Exp. Med., 1921, xxxiv, 407.
[2] *Fahr*, Centrl. f. allg. Path., 1916, xxvii, 1, *Goodpasture*, Jour. Am. Med. Assn., 1921, lxxvi, 1545.

in checking the disease. The second theory is that the condition is due to perverted secretion—*dysthyreosis;* but experimental researches have not adduced definite confirmation of this theory. The third view is that the disease is a general disturbance of the chemistry of the body, the thyroid undergoing a compensatory hyperplasia in endeavoring to overcome the toxic effects of some poison in the system.[1] The fourth theory is that an abnormal nervous system stimulates the thyroid and is in turn excited by the thyroid secretion, thus inciting a vicious cycle.[2] Although the majority of observers believe in the hyperthyroidism theory, the whole question is still under discussion and cannot be regarded as finally settled.[3]

Baumann[4] was the first to obtain by acid hydrolysis an iodine-containing compound from the thyroid gland. Kendall[5] in 1919 by alkaline hydrolysis isolated from the thyroid gland a crystalline substance containing 65 per cent. iodine which he named thyroxin. This has been shown by clinical investigation to be the substance, or one of the substances, which in the thyroid gland controls the rate of metabolism. From further investigation it is probable that the formula assigned by Kendall to thyroxin is not correct, but that it is a derivative of tyrosin instead of indol.[6] It has been shown that one milligram of thyroxin daily will replace that consumed in the body and that fourteen milligrams of this substance must be present in order to maintain the basal metabolism rate at a normal level. Larger quantities definitely raise the basal metabolism above the normal level.[7] The increased metabolic rate which is usually present in exophthalmic goiter may be explained by the presence of an excess of this substance. The administration of iodine lowers the elevated metabolic rate in exophthalmic goiter. The rapid heart action is probably a compensatory process to meet the demands of a greatly increased metabolism. Thus while some of the symptoms of exophthalmic goiter may be induced by thyroid extracts or thyroxin, there are other features of the disease which cannot. The exophthalmos is generally considered as due to sympathetic stimulation, so the general opinion is that the sympathetic nervous system, and possibly the adrenal, are concerned in the classical picture of exophthalmic goiter.

[1] See for study of basal metabolism in exophthalmic goiter, *Means, J. H.*, and *Aub, J. C.*, Jour. Am. Med. Assn., 1917, lxix, 33.

[2] *Wilson, L. B.*, Am. Jour. Med. Sc., 1916, clii, 799.

[3] For studies on the lesions of the thyroid gland and exophthalmic goiter, see *Ewing*, Trans. Assn. Am. Phys., 1906, xxi, 567; and *MacCallum*, Jour. Am. Med. Assn., 1907, xlix, 1158; and the numerous papers by *Marine* and *Lenhart*, Arch. Int. Med., 1909, iv, 440; ibid., 1911, vii, 506; ibid., 1911, viii, 265. For a study of adenomata of the thyroid gland, some of the cases exhibiting a few of the symptoms of exophthalmic goiter, see *Bloodgood, J. C.*, Surg., Gynec., and Obst., 1906, ii, 121. For a presentation of the dysthyreosis theory, see *Klose*, Beitr. klin. Chir. (Bruns), 1912, xxvii, 601. For a study of the relation between the nervous system and the thyroid, see *Oswald, A.*, Cor.-Bl. f. schweiz. Aerzte, 1912, xlii, 1130; *Roussy, G.*, Les lésions du corps thyroide, Paris, 1914; *Launoy, L.*, Thyroide, parathyroides, thymus, Paris, 1914. For studies on iodine content and effects of iodine treatment, see *Cattell, R. B.*, Bost. Med. and Surg. Jour., 1925, excii, 989 and Proc. N. Y. Path. Soc., 1925, N. S. xxv, 128. For a general survey of the subject see *Swale Vincent*, Internal Secretions and the Ductless Glands. New York, 1925.

Eppinger, Die Basedowsche Krankheit, in Lewandowsky's Handbuch der Neurologie, Bd. iv, Berlin, 1913.

[4] *Baumann*, München. med. Wochenschr., 1896, xliii, 309, 1153.

[5] *Kendall*, J. Biol. Chem., 1919, xxxix, 125.

[6] *Harington*, Biochem. Jour., 1926, xx, 293.

[7] *Boothby* and *Sandiford*, Physiol. Reviews, 1924, iv, 69. *Marine*, Physiol. Reviews, 1922, ii, 521.

ADDISON'S DISEASE.

This name is applied to a disease especially characterized morphologically by a peculiar pigmentation of the skin and by certain changes, morphological or functional, in the adrenals. The patients suffer from cerebral symptoms, great prostration, syncope, and derangements of the functions of the stomach and intestines.

The pigmentation of the skin is the symptom which has especially attracted attention. The change in color usually begins and becomes most marked in those parts of the skin which are not covered by the clothing or are naturally of darker color. The rest of the skin afterward changes color, but not uniformly, white patches being left. The color is at first a light yellow or brown; this becomes darker until it is of a dark greenish, grayish, or blackish brown. The mucous membrane of the tongue, lips, cheeks and gums may be similarly pigmented.

As examples of Addison's disease different observers have described cases in which the symptoms and bronzed skin existed without disease of the adrenals; cases in which the bronzed skin was the only lesion; and cases in which the adrenals were diseased without symptoms or bronzed skin.

The Skin.—The discoloration of the skin is due to a deposit of yellowish-brown pigment in the deeper layers of the epidermis, especially in the layer covering the papillæ, and less constantly in the connective tissue of the cutis.

The Brain.—Pigmentation of the gray matter, acute meningitis, chronic meningitis, and distention of the ventricles with serum have been observed.

The sympathetic nerves, especially those which are in contact with the adrenals, may show a variety of changes apparently due to chronic inflammation. Various changes in the nerve cells of the semilunar ganglia have been described.

There may be fatty degeneration of the heart muscles and hyperplasia of the intestinal lymph-nodules and the spleen.

The Adrenals.—The most common lesion of these bodies is a tuberculous inflammation, and this or some other lesion has been found in nearly one-half of the cases. On the other hand, it should be remembered that similar lesions of the adrenals often occur without other indications of Addison's disease. Tuberculous adrenals may be large, hard, and nodular; less frequently of normal size or smaller than normal. On section they may contain cheesy masses surrounded by zones of gray, semitranslucent tissue. Later the cheesy masses may become calcified or they may soften and break down. The grayish zones are composed of tubercle tissue or denser connective tissue.[1]

Other cases have been described in which the adrenals were the seat of carcinoma or of fatty or waxy degeneration. But these lesions,

[1] For a study of experimental tuberculosis of the adrenals and its relations to Addison's disease, see *de Vecchi*, Centralbl. f. allg. Path. 1901, xii, 577.

especially carcinoma of the adrenals, may occur without the manifestations of Addison's disease. The adrenals may be atrophied. They may, however, be normal, and in some such cases lesions of the semilunar and other sympathetic ganglia have been found.

On the whole, the clinical, morphological, and experimental data now available seem to point to lesions of both the sympathetic system and the adrenals as of probable significance in determining this disease.

The hypothesis which is most in favor at present assumes that the adrenals furnish an internal secretion without which normal metabolism cannot be effected, and that lesions of the adrenals or of the sympathetic ganglia and vessels about them, by altering or diminishing this secretion, may lead to the functional and structural changes characterizing the disease.[1] This active principle, which is present in the medullary and chromaffin portion of the adrenal in 1 part in 1000 of the fresh organ, has recently been produced synthetically and found to be a base, chemically designated as methylamino-acetocatechol. The relationship between the medulla of the adrenals and the sympathetic is apparently intimate but is as yet obscure. Complete removal of the adrenals is rapidly fatal. Injection of the extracts after removal of the organs fails to maintain life. The action of extracts of the adrenals or the pure base upon the muscle fibers of arteries leads to an increase in blood pressure.

DIABETES MELLITUS.

This disease involves such defects in metabolism as lead to an abnormal accumulation of sugar in the blood (*hyperglycemia*) and its appearance in the urine (*glycosuria*).[2]

A great variety of lesions have been found in the body after death from diabetes, but few of them, aside from those of the pancreas, appear to be of well-defined significance in this special relationship. The general condition of malnutrition and debility, so often marked in this disease, renders diabetics especially vulnerable to slight injuries or infections, furunculosis, carbuncle, eczema, etc.; gangrene is liable to occur either with or without marked injury in cases of diabetes.[3]

The nervous system may be normal. Peripheral neuritis with or without lesions in the gray matter of the anterior horns is frequent. A terminal pneumonia is not uncommon. The liver may be cirrhotic or fatty. The kidneys may show diffuse nephritis and often a glycogenic infiltration of the epithelium of Henle's loop. A moderate amount of fat is often present in the blood, and fat emboli in the lungs have been described.

The lesions in the pancreas are variable. In about 10 per cent. of patients, especially in the young, no lesion of the pancreas can be demonstrated (Fig. 287). A functional insufficiency must therefore be

[1] For the effects of removal of suprarenal body and the nature of its "active principle," consult *Abel*, Vaughan Anniversary Contributions, 1903, p. 139 (bibl.). Also *Barger*, Natural Bases, New York, 1914, and *Biedl*, The Internal Secretory Organs, New York, 1913; *Bayer, G.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1910, xiv,[2] 1.

[2] For a résumé of metabolism in diabetes, see *Lusk*, Arch. Int. Med., 1909, iii, 1.

[3] For bibliography of diabetic gangrene, consult *Davis*, Jour. Am. Med. Assn., 1898, xxx, 113.

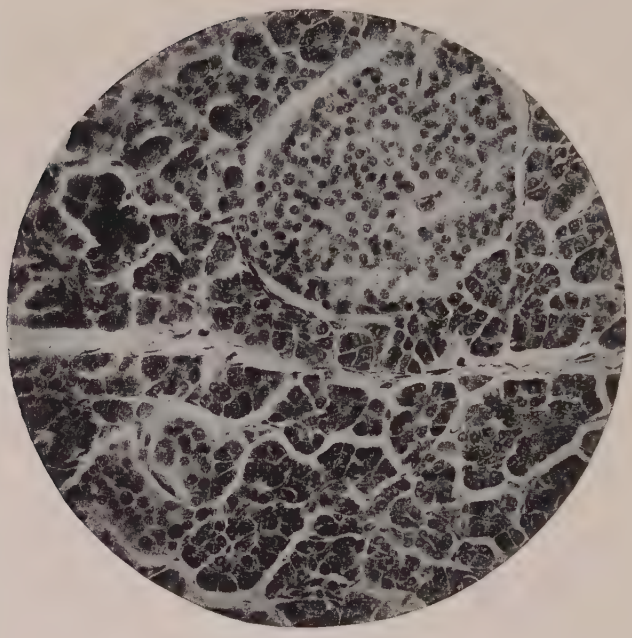


Fig. 287.—Normal Island in a Diabetic. Light Case with Cholecystitis and Pancreatitis. Death Due to Operation. × 200.

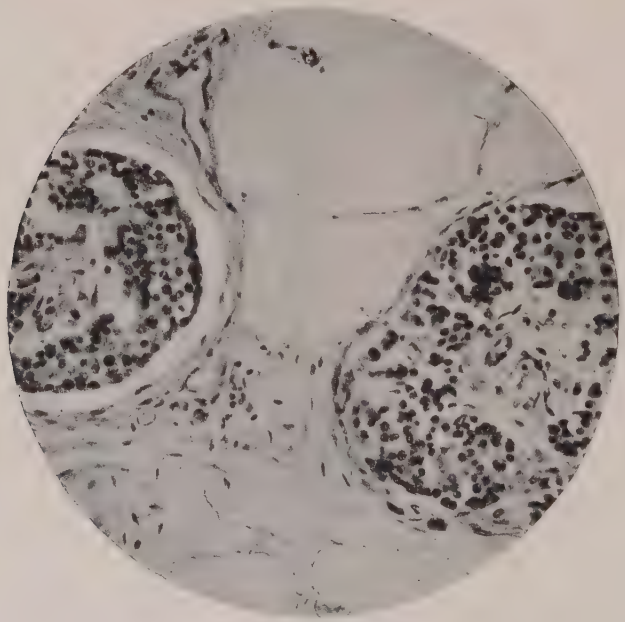


Fig. 288.—Approximately Normal Islands in a Pancreas with Extensive Atrophy and Fibrosis. Severe Diabetes for Several Years. × 200.

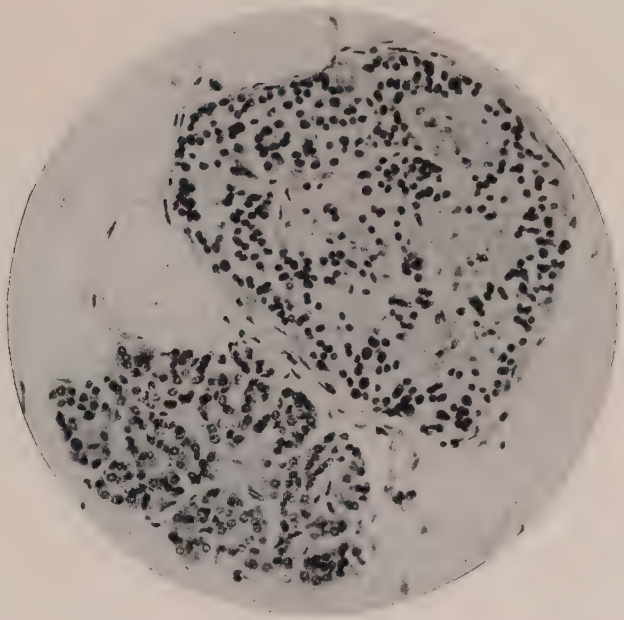


FIG. 289.—ATROPHY OF PANCREAS AND AN INCREASE OF INTERSTITIAL TISSUE IN THE ISLANDS. SEVERE DIABETES FOR SEVERAL YEARS. × 200.

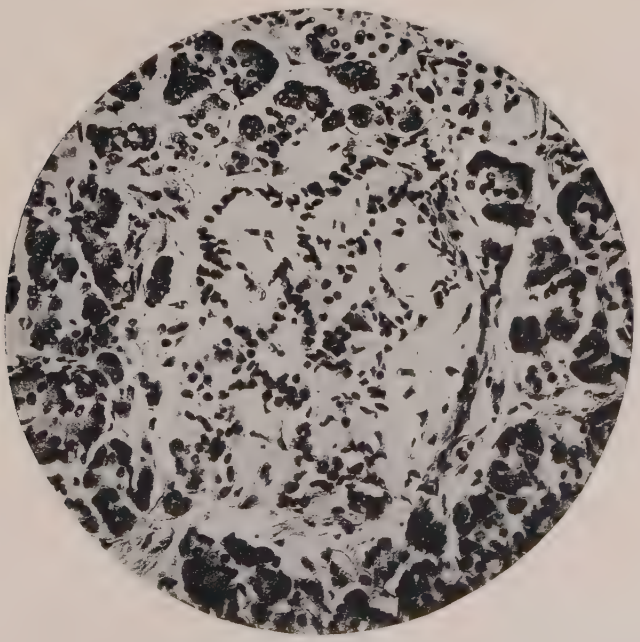


FIG. 290.—HYALINE DEGENERATION AND FIBROSIS OF ISLAND OF LANGERHANS. SEVERE DIABETES IN AN OLD MAN. × 200.

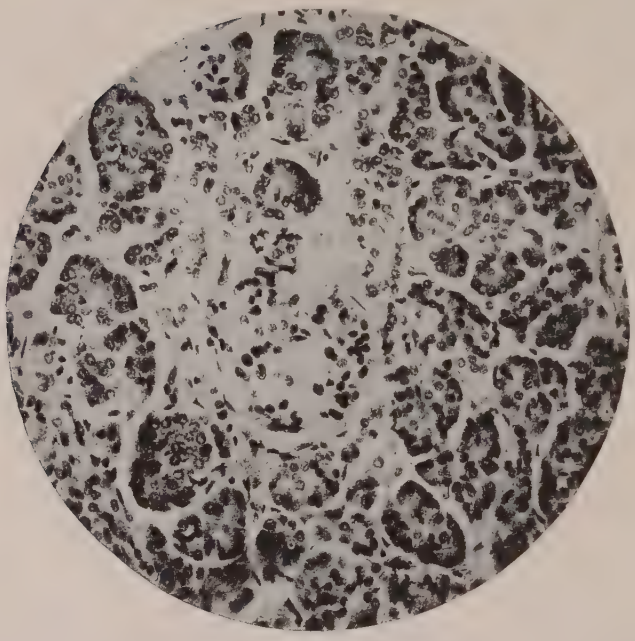


Fig. 291.—Extreme Atrophy with Hyaline Degeneration of Island of Langerhans in a Severe Case of Diabetes. × 200.

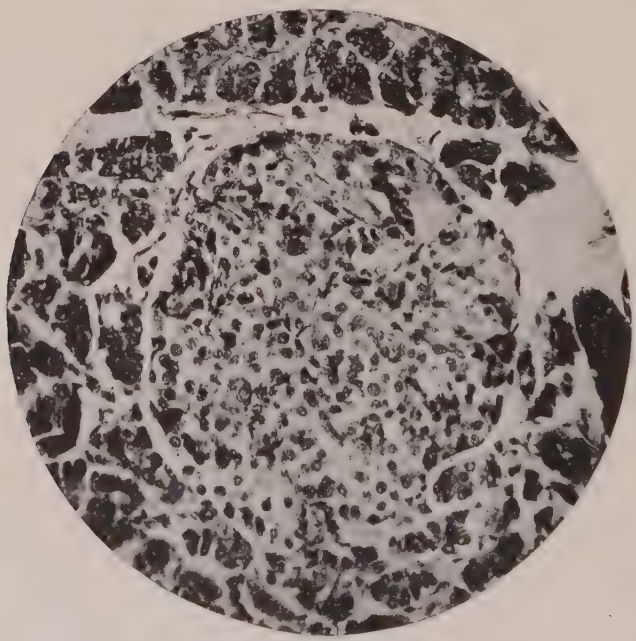


Fig. 292.—Moderate Hypertrophy and Slight Degree of Hyaline Change in the Islands of Man Aged 47. Severe Diabetes for at Least a Year, Gangrene of the Leg, Amputation. Death in Coma. × 200.

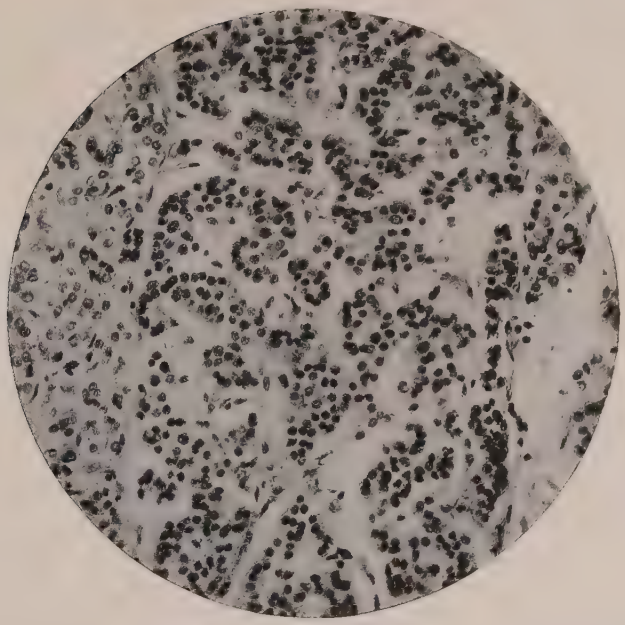


Fig. 293.—Extreme Hypertrophy of Island in a Very Severe Case of Diabetes with No Treatment for Six Years. Blood Sugar 300 to 800 Mgms. Even with 100 or More Units of Insulin. Death in Coma. × 200.

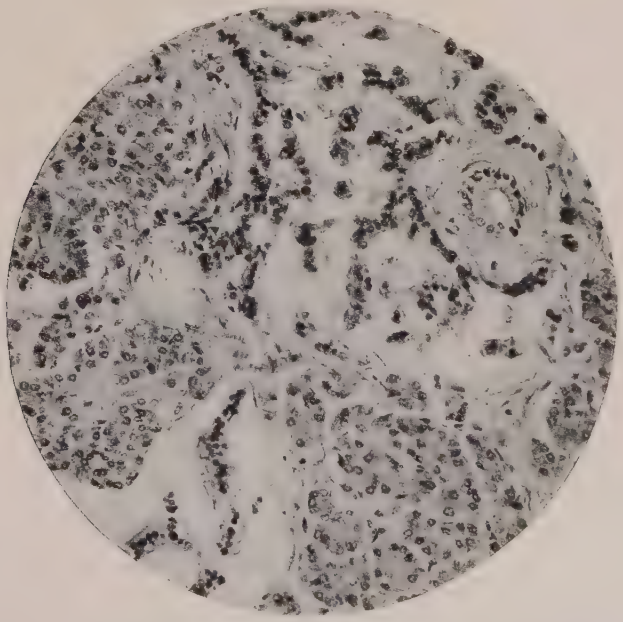


Fig. 294.—Adenoma-like Proliferation of Islands in a Mild Diabetes, Marked Nephritis and Arteriosclerosis. Blood Sugar Not Very High. Death Due to Nephritis. × 200.

assumed. On the other hand there may be a general atrophy with fat replacement and an increase of interstitial tissue especially in old persons (Figs. 288 and 289). Hyaline degeneration and fibrosis of the islands of Langerhans are present in a large proportion of the cases (Figs. 290, 291 and 292).[1] An adenoma-like hypertrophy of the islands is occasionally noted either in light or severe cases of diabetes (Figs. 293 and 294). In all of these photomicrographs the magnification is the same so that the variations in size of the islands are striking. The severity of the diabetes is not always in relation to the destruction of the islands. Tumors, cysts, and calculi in the pancreatic duct have also been found. The attempt to correlate the pancreatic lesions with syphilis has no warrant from the facts.[2] Excision of the pancreas in man or animals causes diabetes. If the animal be pregnant diabetes does not supervene until after delivery, the fetal secretion acting through the placental circulation. Ligature of the ducts causes an atrophy of the acinar structures but not of the islands and no diabetes. If carcinoma develops in the pancreas, the diabetic condition may improve, due, it is claimed, to the sugar-splitting capacity of the tumor cells. In 1922 Banting and Best[3] showed that by ligating the pancreatic duct so as to cause atrophy of the acinous tissue, and after a considerable time extracting the atrophied tissues with saline of an acid reaction, they obtained a fluid which greatly reduced the blood sugar when injected intravenously. The extract so obtained loses its activity when treated with pancreatic juice or boiled. It is only effective if injected intravenously. In their first experiments they allowed ten weeks for the complete degeneration of the acinous tissues. The degenerated pancreas was then removed and sliced in cold Ringer's solution and the gland half frozen and macerated. The solution so obtained was filtered through paper and the filtrate injected intravenously. Dogs completely depancreatized according to Hédon's method[4] were kept alive for long periods when so treated.

Further details need not be given here but Banting and Best have offered the final proof that the islands of Langerhans furnish some substance which enables the body to store sugar, and prevents many if not all of the symptoms of diabetes. Whether other glands such as the liver or organs of internal secretions, such as the adrenals or the thyroid, are in any way correlated with what we call diabetes clinically, is not yet clear. One interesting point is that after the treatment of an active diabetic with insulin, as the product is called,[5] there is evidence that a certain restoration of the function of the pancreas may take place. So far this has been observed only in isolated cases and is possibly accomplished by a compensatory hypertrophy of the remaining islands as is occasionally seen in advanced cases of diabetes (Figs. 293 and 294).

[1] For the relationship of diabetes to lesions of the pancreas, and particularly to lesions of the islands of Langerhans, see *Opie, E. L.*, Disease of the Pancreas, 2d ed., Philadelphia, 1910; for pathological physiology of diabetes, see *MacLeod*, Diabetes; Its Pathological Physiology, London, 1913; and for interesting clinical statistics, see *Joslin*, Treatment of Diabetes Mellitus, 3d ed., Philadelphia, 1924. See also *Cecil, R. L.*, Jour. Exper. Med., 1909, xi, 266.

[2] See *Rosenbloom*, Jour. Am. Med. Assoc., 1917, lxviii, 1232.

[3] *Banting* and *Best*, Jour. Lab. & Clin. Med., 1922, vii, 251, 464.

[4] *Hédon*, Compt. rend. Soc. de biol., 1909, xlvi, 421.

[5] For a full discussion of the insulin question see *MacLeod*, Physiol. Reviews, 1924, iv, 21.

Diabetes mellitus may be associated with hemochromatosis and cirrhosis of the liver—so-called "bronzed diabetes" (page 69).[1]

Diabetes Insipidus.

The passage of large quantities of urine of very low specific gravity is a condition—for it can hardly be called a disease—which is occasionally met with in persons otherwise in apparently good health. Functional tests of the kidneys show normal excretory power, and histological examination of these organs lend no support to the view that the polyuria is due to any structural alteration in them.[2]

The theory at present accepted is that the condition is caused by some lesion of the hypophysis cerebri, for it has frequently been observed that tumors of, or alterations[3] in this organ result in polyuria. This assumption has been based partly on the observations originally made by Schaefer[4] that the administration of hypophyseal extract caused diuresis and that mechanical or thermal stimulation of the hypophysis in living animals causes a polyuria, and partly on the fact that polyuria is a somewhat frequent clinical symptom in acromegaly and is occasionally seen in hypophyseal adiposity. It has long been known that certain diseases of the brain,[5] especially intracranial tumors[6] and cerebral syphilis, are frequently met with in cases of diabetes insipidus. The occurrence of this condition with bitemporal hemianopsia has led to the investigation of the causes of this rare eye disease. The lesions found have usually been syphilitic meningitis, basal tumors, and injuries of the base of the brain.

Diabetes insipidus has also been noticed to follow a carcinomatous metastasis into the pars posterior, the normal structure of which was almost entirely destroyed. The pars intermedia and the pars anterior remained intact. In many cases of diabetes insipidus in which no autopsy has been performed, enlargements, deformation, or erosion of the sella have been noticed in x-ray pictures. An extraordinary sugar tolerance is found in diabetes insipidus; even as much as 450 grams of glucose may be given at one time without the appearance of sugar in the urine. Dunn[6] calls attention to the interesting fact that while the sugar was being taken the quantity of urine was markedly diminished. From these facts it has been assumed that diabetes insipidus is due to a hyperfunction of some portion of the hypophysis, possibly the pars intermedia.

GOUT.

The characteristic lesion of gout is the presence of an abnormal amount of uric acid in the blood and the deposit of urate of sodium in the articular cartilages, the ligaments of the joints, the ears, and the

[1] See *Opie*, Jour. Exper. Med., 1899, iv, 279; *Sprunt, T. P.*, Arch. Int. Med., 1911, viii, 75.
[2] *Christie, C. D.*, and *Stewart, G. N.*, Arch. Int. Med., 1917, xx, 10.
[3] *Weber* and *Schmidt*, Am. Jour. Med. Sc., 1916, clii, 892.
[4] *Schaefer*, Jour. Physiol., 1899–1900, xxv, 87.
[5] *Newmark, L.*, Arch. Int. Med., 1917, xix, 550.
[6] *Dunn*, Am. Jour. Med. Sc., 1914, cxlviii, 214.

eyelids. Inflammatory changes may be associated with the deposits in the joints. There appears to be an hereditary predisposition to the disease.[1]

The most frequent situation of the gouty deposit is the metatarsophalangeal joint of the great toe. The cartilage may be infiltrated or encrusted with the deposit. These masses of urates, often called *chalkstones* or *tophi*, may appear upon the surface by the ulceration of the skin (Fig. 295).

A very important feature of gout is that patients with the gouty diathesis are especially liable to derangements of digestion and to certain chronic inflammations, such as chronic inflammation of the arteries, the

FIG. 295.—LESIONS OF GOUT IN THE HANDS.
Some of the smaller tophi at the finger tips are ulcerating.

bronchi, and the kidneys. Cardiac hypertrophy may be associated with the arteriosclerosis. The interstitial tissue, especially in the pyramids of the kidney, may be infiltrated with the urates.

The nature of the disturbances of nitrogenous metabolism underlying the manifestations of gout is not yet clear, nor are we able to estimate the influences of faulty elimination or local tissue alterations upon accumulations of uric acid in the body. Nor is the relationship plain of local inflammatory processes to the gouty deposits.

SUNSTROKE. (Insolation; Heat Exhaustion.)

Persons exposed, while at work or when exhausted, to the sun or to high temperatures are liable, especially if of intemperate habits, to sud-

[1] For study of gout, see *Minkowski*, Die Gicht, Vienna, 1903.

den prostration, often associated with cardiac failure, asphyxia, convulsions, and coma. Death in many cases soon ensues.

After death, decomposition sets in early and progresses rapidly. The blood usually remains fluid.

The brain and its membranes are in some cases congested, in others not. There may be an increased amount of serum beneath the pia mater, or small and thin extravasations of blood beneath the pia mater and between the pia and dura mater. Chromatolysis of the ganglion cells has been described by Van Gieson[1] and others. The thoracic and abdominal viscera may be congested; albuminous degeneration may be evident in the liver and kidneys.

In the cases in which cerebral symptoms are protracted for a number of days the lesions of meningitis have been found after death.

According to Cramer,[2] persons surviving for some time the first severe effects of the heat may suffer important alterations in certain nerve fibers of the brain.

SCORBUTUS. (Scurvy.)

This disease is caused by an insufficient amount of vitamin C in the food.[3] The lesions are variable, the most common being anemia; extravasation of blood in the skin, subcutaneous tissue, and muscles; swelling and ulceration and bleeding of the gums. Small and sometimes extensive hemorrhages are apt to occur in the mucous membranes and on serous surfaces. Small ulcers may form in the mucous membranes. Fatty degeneration of the heart, liver, and kidneys is not uncommon. The spleen may be large and soft. No constant characteristic changes have been discovered, either in the blood-vessels or the blood, which would satisfactorily account for the extravasations and other lesions.

The body is apt to decompose early. The skin may be mottled with small and large purple, blue, brown, or blackish spots produced by degenerative changes in the extravasated blood in the cutis. Sometimes ulcers are produced by the perforation of effused blood on to the surface. The joints may be inflamed, may contain serum or blood. Rarely the hemorrhages are followed by destruction of the cartilages and ends of the bones. Very rarely there is hemorrhage between the periosteum and bone, and in the bone itself, producing softening and destruction of the bone, and separation of the epiphyses. The sternal ends of the ribs are the most frequent seat of this change. Albuminous degeneration of the heart, liver, or kidneys, and enlargement of the spleen, are common.

Infantile Scorbutus.—Infants under two years may develop similar anemia and tendency to hemorrhages. The most common location of the hemorrhages is beneath the periosteum of the bones of the lower extremities, especially of the femora, with separation of the lower epiphy-

[1] *Van Gieson*, Toxic Basis of Neural Diseases, New York State Hosp. Bull., 1896, i, 407; also *Lambert, A.*, Med. News, 1897, lxxi, 97.

[2] *Cramer, A.*, Centralbl. f. allg. Path., 1890, i, 185.

[3] *Hess, A. F.*, Jour. Am. Med. Assn., 1921, lxxvi, 693.

ses.[1] There may be hemorrhages in the skin and subcutaneous tissues, the eyelids, and orbit, and in the internal organs. Hemorrhagic inflammation and ulceration of the gums are usually limited to infants having teeth and to portions of the jaw in which teeth are apparent or just about to come into view.[2]

That some forms or phases of scorbutus are of infectious nature is not improbable, but definite data in this direction are wanting.

BERIBERI.

Beriberi is a disease of warm climates, due to the use of rice from which the hulls have been removed. The hulls contain a substance called vitamin B, which is indispensable to the body. If the disease is not too far advanced it can be cured by adding fresh meat to the dietary.[3] The lesions are often not well defined. There are in some cases subcutaneous edema and dropsy. There is often degeneration of the peripheral nerves and of the heart and voluntary muscle.

PELLAGRA.

Pellagra is a disease especially of the rural districts, long prevalent in Europe, and now of serious extent and import in the southeastern portions of the United States. It is characterized by protean symptoms and lesions of the nervous, digestive, and cutaneous systems, such as neurasthenia, ataxia, and paralysis; erythema and dermatitis; and profound disturbances of nutrition. It is not communicable, nor is evidence at hand that it is infectious. Its inciting agents or factors are not definitely known. But unbalanced food ration, some toxic substance or organism in the spoiled maize or Indian corn which is often an important feature in the dietary of those affected, and many other factors and agencies have been considered as of possible etiological importance in the disease.[4]

ACROMEGALY.

This disease, which was first recognized by Pierre Marie in 1886, is characterized by an enlargement of the bones[5] and soft parts of the face and extremities, and occasionally also of the internal organs. The symptoms are headache, muscular weakness, a loss of sexual activity, glycosuria, presumably due to pressure on the posterior lobe of the hypo-

[1] For details of bone lesions, see Möller-Barlow disease, page 1075.

[2] For a study of scorbutus in infants, Barlow's Disease, which was first recognized in the United States by Northrup, consult *Northrup* and *Crandall*, New York Med. Jour., 1894, lix, 641. See also The American Pediatric Society's Collective Investigation on Infantile Scurvy in North America, Tr. Am. Pediat. Soc., 1898, x, 5. For a study of histological changes, consult *Jacobsthal*, Zieglers Beitr., 1900, xxvii, 173.

[3] *Vedder*, Beriberi, New York, 1913; *Funk*, Die Vitamine, Wiesbaden, 1914; *McCollum, E. V.*, Jour. Am. Med. Assn., 1917, lxviii, 1379.

[4] For summaries and bibl., see *Roberts*, Pellagra, London, 1912; also résumé by *Bartholow*, New York Med. Jour., 1913, xcviii, 1262; and First Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School by *Siler* and *Garrison*, Am. Jour. Med. Sc., 1913, cxlvi, 42, 238; *Goldberger*, Jour. Am. Med. Assn., 1916, lxvi, 471. For study of epidemiology of the disease see *Jobling, J. W.*, and *Petersen, W. F.*, Jour. Infect. Dis., 1916, xviii, 501. For studies on the experimental production of pellagra, see *Chittenden* and *Underhill*, Am. Jour. Physiol., 1917, xliv, 14.

[5] For details of bone lesions, see page 1065.

physis, and a general failure of mental powers, probably correlated with the pressure which the growth exerts on the brain. The glycosuria occurs only during the periods of functional hyperplasia; at other times the assimilation limit for carbohydrate is extraordinarily high. In all the published cases of acromegaly a tumor of the hypophysis has been present, and though many of these neoplasms have been called sarcomata, in all probability this is due to a lack of recognition of the peculiar anatomy of the gland. According to Fischer,[1] all such tumors occurring in acromegaly belong to the true adenomata. The cells which form these adenomata are usually of the eosinophile type, though tumors largely composed of basophile cells have been seen; the granules, however, are often less definite than in the cells of the normal gland. Occasionally an adenomatous growth may develop at a site apart from the gland. Erdheim has described one case in which the tumor was situated in the body of the sphenoid bone, and other cases are on record in which the enlargement was chiefly in the pharyngeal remnant of the hypophysis. Persistence of the thymus gland is not infrequently observed in connection with acromegaly and an atrophy of the thyroid is also to be noticed. Even more frequent than the changes in the two glands mentioned above are atrophy of the testicle with changes in the epithelium of the germinal tubules and the interstitial cells of Leydig in men, and a cessation of the formation of ova in the ovary with ultimate atrophy of the primordial follicles in women. In connection with these changes there is also very frequently noticed an obliteration of the secondary sexual characteristics. Hyperplasia of the suprarenal gland is not infrequent. The exact condition which underlies the disease is not as yet completely determined. Whether the changes in the sexual organs or in the thymus and thyroid have anything to do with the production of hypersecretion from the hypophysis or with the growth of the adenomatous masses found therein, is not as yet settled; but it is evident from what is now known of the disease that it cannot be considered as due wholly to the changes in the pituitary gland, but that it is correlated with changes in the other glands of internal secretion. Acromegaly may, therefore, be fairly considered as belonging to the group of polyglandular diseases. The very favorable results which have been noted following the partial extirpation of a tumor of the anterior lobe of the hypophysis show, however, that this is the most important gland in the production of the symptom complex.[2]

HYPOPHYSEAL ADIPOSITY.

Another condition connected with alterations in the hypophysis is the so-called *hypophyseal adiposity* or *dystrophia adiposogenitalis*. The persons afflicted show an increasing adiposity, diminished secretion of sweat, atrophic changes in the skin in conjunction with hypoplasia of the male or female genitalia, and alteration in the distribution of the

[1] *Fischer, B.*, Hypophysis, Akromegalie und Fettsucht, Wiesbaden, 1910.

[2] For an excellent résumé of acromegaly, with cases and bibl., see *Brooks*, Arch. Neurol. and Psychopath., 1898, i, 485; also *Lewis*, Bull. Johns Hopkins Hosp., 1905, xvi, 157. For physiology and pathology of the hypophysis, see *Biedl*, Innere Sekretion, Berlin, 1913; and *Cushing*, The Pituitary Body and its Disorders, Philadelphia, 1912.

pubic and axillary hair. Connected with these changes are symptoms which may be best described as infantilism. The pathological lesion found in two-thirds of the cases is a tumor of the hypophysis, which in contrast to the condition in acromegaly, originates not in the glandular anterior portion, but rather in cells derived from the hypophyseal duct. Hence a variety of tumors have been found: squamous-cell carcinomata, sarcomata, gliomata, teratomata, and the like. The only vital factor seems to be the injury of the posterior lobe and the infundibular region. Other processes also, such as injury, hydrocephalus, tumors of the base of the brain, can give the same symptoms. Whether the changes are due to a lack of the neurohypophysis or to an interference with the absorption of secretion from the anterior lobe is still doubtful. Pressure on the posterior lobe causes symptoms connected with the genital glands; still stronger pressure causes adiposity. It is to be remembered in this connection that adiposity frequently occurs also in connection with acromegaly. Cushing has called attention to the fact that in hypophyseal adiposity the assimilation capacity of the body for glucose is extraordinarily increased, so that it is almost impossible to produce a glycosuria in these patients by the administration of a large quantity of sugar, even up to 500 grams of glucose. In contrast to this is the glycosuria frequently observed in acromegaly. The occurrence of many of these physical characteristics in connection with the removal of the testicles before the age of puberty, as in eunuchs and persons of certain religious sects in Russia, has led to the suggestion that the condition is primarily an atrophy of the genital glands; but this is shown not to be true by the fact that out of thirty-two cases examined, in only twelve was genital atrophy found. The important part played by the hypophysis has been demonstrated by the experimental work of Biedl and Cushing, who have proved that the removal of the posterior and a portion of the anterior lobe of the hypophysis in young animals produces a picture quite comparable with that seen in man. The animals grow fat, are of low mentality, and show a hypoplasia of the genital organs. A more plausible explanation of the cause of the disease is, therefore, that it is a hypopituitarism produced by interference with the absorption or production of the specific glandular secretion.

GIGANTISM.

Another form of disease which is correlated with acromegaly, yet in which other factors also dominate the picture, is gigantism. In this there is evidently a hypersecretion of the hypophysis, a primary atrophy of the genital glands, and, probably in addition in some cases, a hyperactivity of the thyroid. The condition is actually an anomaly of the growth of bone, which leads to a body length exceeding the average of the race. *X*-ray examinations of the skeleton show that the epiphyseal junction may remain uncalcified during the progress of growth and that there is also an hypertrophy of the bony substance of the long bones. The spinal column is often kyphotic or scoliotic. The face and ex-

tremities frequently show suggestions of acromegalic alterations, such as prominent cheek bones, marked superciliary arches, projections of the lower jaw, thickening of the bones of the skull, increase in the size of the sella turcica, and changes in the hands and feet, consisting in a thickening of the end of the bone with growth in length and breadth.[1] Enlargement of the thyroid has been mentioned. Other striking changes are those of the genital glands; there is diminution in sexual activity, lack of potency in man, absence of menstruation and ability to conceive in woman. The internal genital organs are commonly atrophic, and the external organs, such as the penis, vulva, and vagina, are imperfectly developed. The distribution of the hair on the body is abnormal; there is often absence of the pubic and axillary hair and a very small development of the beard in men. The body is frequently more adipose than is normal for the age of the person affected. The disease is more common in men than in women and begins primarily at the age of puberty. Some of the cases ultimately develop a full picture of acromegaly. Alterations in the hypophysis are not infrequent, and may consist in a mere hyperplasia of the glandular substance, or in the formation of adenomata or vascular tumors, while in some cases sarcomata or epitheliomata have been met with. The hypophysis may, however, be both macroscopically and microscopically normal. The mental activity of these giants is frequently very slight, almost always lower than normal. Not all cases of gigantism, however, belong in this class, for some of these people are perfectly normal mentally and show no evidence of pathological change in any of the organs mentioned, that is, the hypophysis, thyroid, and genital glands.

DWARFISM.

The study of a certain small group of dwarfs in which the body is well proportioned and the intelligence fairly well developed has led to the conclusion that a diminished function of the anterior portion of the hypophysis may explain the condition. In these individuals the epiphyseal junctions remain cartilaginous; just as in the hypophyseal forms of gigantism, the distribution of the hair on the body is infantile in type and the genital organs also remain undeveloped. In some of the cases there has been hemianopsia or optic-nerve atrophy, severe headache, polyuria, and other symptoms which, with enlargement of the sella turcica, would lead to the conclusion that a tumor was developing in the site of the hypophysis, accompanied by a diminution in the activity of the anterior lobe.[2]

PURPURA.

This name is applied to a variety of conditions in which extravasations of blood are present in the skin or the mucous and serous membranes.

Hemorrhages, particularly from the mucous membranes, may be severe and even fatal. This condition is often called *purpura hæmorrhagica.*

[1] For further details, see page 1065.
[2] For further details, see page 1063.

The ecchymoses characteristic of purpura may occur as a result of poisoning with certain drugs, and with snake venom; in various cachectic conditions; in diseases of the nervous system; in rheumatism; in gastro-intestinal disorders, especially of children. The local ecchymoses in pyemia are sometimes classed as a form of purpura; and in these, bacteria, especially the pyogenic forms, may be demonstrable.[1]

Either from the direct action of poisons; or through degeneration of the endothelium of the smaller vessels; or as the result of capillary embolisms, extravasation of blood may take place.[2]

LYMPHATIC CONSTITUTION. (Constitutio Lymphatica: Status Lymphaticus.)

Sudden death after the administration of ether or after slight trauma is frequently correlated with a pathological condition in which the chief lesion is a hyperplasia of the lymph tissue of the body with hypoplasia of the heart and aorta. The thymus is often enormously enlarged and may reach such a size as to compress the bronchi and large vessels of the upper mediastinum. (See Fig. 298 and 299, and section on the Thymus, page 586.) The pharyngeal, thoracic, and abdominal lymph-nodes are most frequently involved in the hyperplasia, the process infiltrating the surrounding connective tissue. The spleen shows hyperplasia of the follicles but is usually not greatly enlarged.

Clinically, a diagnosis can be made in male adults if with lymphoid enlargement there is connected a feminine type of body outline, with scanty hair on the face, axilla, and sternum, and a feminine distribution of the pubic hair, a slender thorax, a rounded contour of the upper arms and thighs with arching of the latter, and hypoplasia of the external genitals. In women the hair on the body may be scanty, though usually there is more than normal on the face; there is also hypoplasia of the genital apparatus and slender thorax and extremities. In children the diagnosis is difficult, but may occasionally be made by *x*-ray demonstration of an enlarged thymus. Such children are usually pale and feeble and show general lymphatic enlargement. Rickets, tuberculosis, and syphilis are common accompaniments of the disease.[3]

The theory has been advanced[4] that sudden death in status lymphaticus is due to one of two causes, of which the first and most frequent is an anaphylactic reaction due to sensitization of the body by a specific nucleoprotein formed in the lymph-nodes as the result of necrosis of numbers of germinal follicles; if, before the incubation period has expired the tissues are again subjected to the action of the same protein formed in the same type of tissue in response to an apparently trivial injury, the

[1] For a more detailed consideration, in the light of recent studies, of cases often grouped under the name "Hemorrhagic Infections," consult *Honl, I.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, i, 793 (bibl.).

[2] *Duke, W. W.*, Arch. Int. Med., 1912, x, 445; and *Osler*, Brit. Med. Jour., 1914, i, 517.

[3] For a study of the lymphatic constitution and its relationship to sudden death, see *Ewing*, New York Med. Jour., 1897, lxvi, 37; *Bartel* and *Bauer*, Status Thymico-Lymphaticus u. Status-Hypoplasticus, Leipzig, 1912; *v. Neusser*, Zur Diagnose des Status Lymphaticus, Wien, 1911 (contains reference to work of Norris, page 228); *Paltauf*, Wien. klin. Wchnschr., 1889, ii, 147; 1890, iii, 24; and *Emerson, H.*, Arch. Int. Med., 1914, xiii, 169.

[4] *Symmers, D.*, Am. Jour. Dis. Child., 1917, xiv, 463.

anaphylactic reaction is completed. A second cause is the rupture, either spontaneously or following apparently trivial injury, of a hypoplastic cerebral vessel, the deficiency in the vessel wall being most noticeable in the muscular coat.

Lymph-Nodes and -Nodules.—The pharyngeal, thoracic, and abdominal lymph-nodes are most frequently involved in hyperplasia, the new cells often infiltrating the surrounding tissue. There may be hyperplasia of the tonsils, of the cervical, mediastinal, axillary, and abdominal lymph-nodes, as well as of the lymphatic tissue of the gastrointestinal canal (Fig. 296).

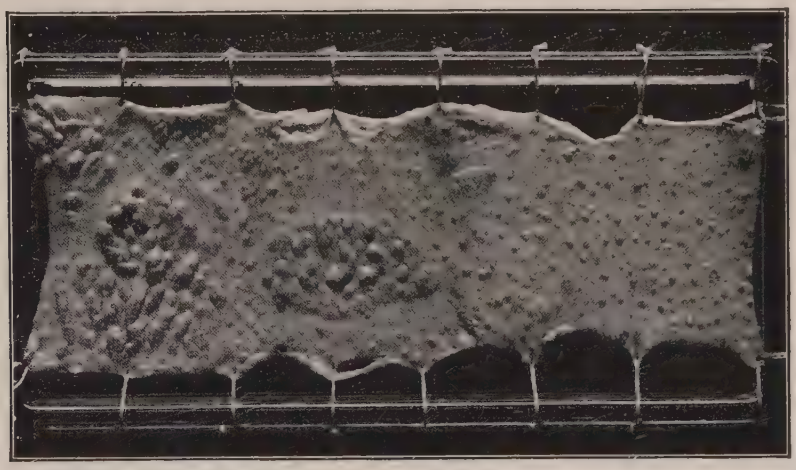


FIG. 296.—HYPERPLASIA OF LYMPHOID TISSUE OF THE INTESTINE IN STATUS LYMPHATICUS.

The *thymus* may be congested and large and soft from hyperplasia. It sometimes exerts such pressure on the adjacent bronchi and large vessels as seriously to impede the action of the heart and lungs.

The *spleen* may be moderately enlarged from hyperplasia, especially of the lymphoid tissue of the Malpighian bodies, and it may be congested.

FEVER. (Pyrexia.)

The heat of the body is derived from tissue metabolism. The heart, the muscles, the liver, and other abdominal organs are the great sources of heat production. The temperature of the body under normal conditions is maintained within narrow limits by the heat-regulating mechanism which preserves the balance between heat production and heat loss effected largely through the skin and respiratory surfaces.

Fever may be defined as a general disturbance of metabolism, usually due to infection or various forms of intoxication, which leads to a rise of the temperature within the body.

The rise of temperature in fever depends primarily upon an increase in the metabolic combustion. Oxygen is used in larger amount than is

usual, while the combustion products, carbonic acid, and the nitrogenous substances, urea, uric acid, etc., are excreted in greater abundance. This increased combustion is usually associated with disturbances of digestion and assimilation of food, so that the abnormal heat production is effected largely at the expense of the body proteins of the various tissues and organs concerned in metabolism.

But with the increased heat production there usually occur, in the earlier periods of fever, such disturbances in the vasomotor control of the cutaneous blood-vessels as lead to their contraction. Thus, heat elimination is retarded. In later periods the vessels of the skin may dilate so that, in spite of its persistent dryness and lack of the cooling effect of sweat evaporation, there is an excessive loss of heat from this source. This is not sufficient, however, to balance the excessive heat production. We need not consider here the various subjective and objective phenomena characteristic of the febrile condition. The height of temperature varies in fever, seldom exceeding 42° C. (107.6° F.), and is usually much less than this. Even this temperature, if it lasts for a few hours, may induce alterations in the cell protein and thus cause death.

In the great majority of cases fever is due to the presence in the body of deleterious substances, either introduced from without, or, more commonly, produced within the body. These are most often formed in infections, and arise either from the growth in the tissues of pathogenic microorganisms or from the disintegration of their bodies; that is, they are *toxins* or *endotoxins*. But there is abundant evidence that fever is not infrequently due to perverted metabolism of the tissue cells, leading to the formation of toxic substances. Such self-engendered substances are called *autotoxins*. The pyrexia of sunstroke is believed to be an example of this phase of autointoxication.

Similarly it is known that certain drugs—cocaine, caffeine, purin bases, phosphorus,—various bacterial toxins, and organic substances—proteins, leucocytic proteoses, ferments, etc.—introduced from without may induce fever.[1]

Exactly how these various substances act in the incitement of fever is unknown. But one assumes that the cell metabolism is disturbed by the poison, while the heat-regulating mechanism is so modified that the normal balance is overthrown. That the nervous system may play an important rôle in these disturbances is indicated by the fact that more or less persistent elevations of temperature may follow puncture or hemorrhage in the corpus striatum or lesions of the bulb or certain other affections of the nervous system.[2]

[1] See *Vaughan*, Protein Split Products, Philadelphia, 1913.

[2] For a study of fever and allied conditions, see *Chantemesse* and *Podwyssotsky*, Les Processus généraux, Paris, 1901; see also *Krehl*, Clinical Pathology, Trans. by Hewlett, Philadelphia, 1905.

For metabolism in fever, see *MacCallum, W. G.*, Arch. Int. Med., 1908, ii, 568; *Hort, E. C.* and *Penfold, W. J.*, Proc. Roy. Soc., London, 1912 (B), lxxxv, 174; *Jona, J. L.*, Jour. Hyg., 1916, xv, 169; and *Gibson, R. B.*, Philippine Jour. Sc. (B), 1914, viii, 475.

CHAPTER XIII.

THE LESIONS IN CERTAIN FORMS OF DEATH FROM VIOLENCE: SUDDEN DEATH.

The Lesions in Certain Forms of Death from Violence.

SUFFOCATION—ASPHYXIA.

By suffocation is meant that condition in which, without direct pressure on the larynx or trachea, air is prevented from penetrating into the lungs. The interruption of the function of respiration which is thus brought about induces the condition known as *asphyxia*. In this way many deaths from drowning and strangulation take place.

The ways in which the supply of air may be cut off from the lungs are various. The mouth and nose may be closed by the hand, by plasters and cloths, by wrapping up the head in cloths, by covering the face with earth, hay, grain, etc. Foreign bodies may be introduced into the mouth, pharynx, and larynx. Blood may pass into the trachea from an aneurysm or from a wound. The glottis may be closed by inflammatory swelling. Vomited material may lodge in the larynx.

On the other hand, injury or disease of the medulla oblongata, or paralysis or spasm of the muscles of respiration from drugs, tumors pressing upon the air passages, or diseases of the lungs themselves, or irrespirable gases which exclude oxygen from the lungs, may induce asphyxia.

External Inspection.—The body should be examined for marks of violence, the cavities of the mouth and nose for foreign substances.

The face may be livid and swollen or present a natural appearance. The conjunctiva may be congested and ecchymotic. There may be small ecchymoses on the face, neck, and chest. The mouth may contain frothy blood and mucus. The tongue may be protruded.

Internal Examination.—*The brain* and its membranes may be congested, or anemic and edematous, or unchanged. *The blood* throughout the body is usually dark-colored and fluid.

The larynx may contain foreign bodies which have induced the suffocation. The mucous membrane of the larynx, trachea, and bronchi may be congested and sometimes ecchymotic: these passages contain frothy blood and mucus. *The lungs* are usually congested and edematous, but sometimes do not differ from their ordinary appearance. There may be small patches of emphysema near the surface of the lungs. Sometimes, especially in infants, small ecchymoses are found in the costal and pulmonary pleura.

The heart usually presents its right cavities full of blood, its left cavities empty; but to this there are frequent exceptions.

The abdominal viscera are usually congested.

DEATH FROM STRANGULATION—HANGING.

Strangulation is effected by the weight of the body in hanging, by pressure on the neck with the hands or by some other object, or by constriction of the neck with a cord or ligature of some kind. Death usually occurs by asphyxia, or by asphyxia combined with the effect of the cutting-off of the blood supply to the brain by pressure on the large vessels of the neck. In some cases of hanging, death ensues as a result of fracture or dislocation of the cervical vertebræ.

External Inspection.—The face may be livid and swollen, the eyes prominent, the lips swollen, and the tongue protruded. These appearances are, however, often absent. Erection of the penis, ejaculation of semen, and evacuation of feces and urine are frequently observed.

In many cases marks are left upon the neck by the objects which have directly produced the strangulation. In cases of hanging, the mark about the neck varies considerably in position, direction, and general characters, depending upon the kind of ligature employed, the time of suspension, period after death at which the observation is made, etc. The most common mark left by a cord about the neck is a dry, dense, brownish furrow, whose breadth corresponds but in a very general way with the diameter of the cord. In some cases, according to Tidy and others, there may be no mark at all if the hanging be quickly accomplished with a soft ligature and the body cut down immediately after death. There may be abrasions and ecchymoses of the skin at the seat of ligature.

In cases of strangulation by the fingers the marks on the neck may correspond in a general way to the shape of the fingers.

The application of the same forces immediately after death may produce the same marks as when death is induced by them.

Internal Examination.—*The brain* and its membranes may be congested, or there may be extravasation of blood, or there may be no abnormal appearances.

The Neck.—In some cases there is effusion of blood beneath the ligature, rupture of the cervical muscles, fracture of the os hyoides and the cartilages of the larynx, fracture and dislocation of the cervical vertebræ, rupture of the internal vertebral ligaments and of the inner and middle coats of the carotid arteries. Similar changes may be produced in the dead body by the use of great violence.

If death occur from asphyxia, the internal lesions are similar to those described above. In some cases—for example, where death has occurred from fright or shock—the results of post-mortem examination are entirely negative.

DEATH FROM DROWNING.

In examining the bodies of persons who are supposed to have been drowned, it is necessary to bear in mind a number of questions which may arise: Whether the person came into the water alive or dead? How long a time has elapsed since death? Whether the person has committed suicide, or was drowned by accident, or was murdered? These questions are to be solved sometimes certainly, sometimes with probability, sometimes not at all, by the post-mortem examination. Persons dying in the water, to which condition the term drowning is commonly applied, may die from asphyxia, from exhaustion, from fright or syncope, from disease of the heart, apoplexy, injuries, etc. While in the majority of cases asphyxia is a predominant or important factor in death by drowning, the conditions under which death occurs are so apt to be complex that in the minority of cases only are the lesions of

pure asphyxia found after death, while in most cases the bodies present the more or less well-marked lesions of asphyxia together with those indicative of complicating conditions. There are no post-mortem conditions which alone are absolutely characteristic of drowning, and it is only by considering all the facts elicited by the autopsy together that any just conclusion can be arrived at. It should always be borne in mind, moreover, that even the most characteristic of the evidences of drowning are apt to be modified or to disappear as decomposition goes on.

External Inspection.—Post-mortem rigidity usually sets in early, sometimes immediately after death. Decomposition progresses, especially in summer, with unusual rapidity in bodies which have been removed from the water. Frequently, but by no means constantly, the peculiar roughening of the skin, known as goose-skin (*cutis anserina*), is found, but this may occur after death from other causes. A light, lathery froth, either white or blood-stained, is frequently seen about the mouth and nostrils within twelve to twenty-four hours after removal of the body from the water, but it may be absent, and may be seen after death from other causes. After the body has lain for several hours in the water (twelve to twenty-four) the thick skin of the palms of the hands and soles of the feet may become macerated and thrown into coarse wrinkles, just as it may after prolonged soaking during life, or in a dead body thrown into the water. The penis and nipples may be retracted, and the scrotum shrunken, but this is not constant nor characteristic.

If the person has struggled in the water and clutched at objects within his reach, there may be evidences of this in excoriation of the fingers or in the presence of sand, weeds, etc., under the nails or grasped in the hands.

External marks of injury, bruises, etc., should be sought for, since persons in falling, or on being thrown into the water with homicidal intent, may have died from the violence, and not, strictly speaking, from drowning. It should also be borne in mind in such complex cases that injuries, not in themselves fatal, may, when the body is in the water, prove so on account of the inability of the person to rescue himself or gain time for recovery from the injury, and that then the struggle for breath may be but slight, and the more prominent signs of drowning but little marked.

Internal Examination.—*The Brain.*—Congestion of the brain and its membranes is found only in a small proportion of cases.

The blood, when death occurs from asphyxia, is usually fluid throughout the body and of a dark color, as in asphyxia from other causes.

The Air Passages.—In persons who die from asphyxia the mucous membrane of the larynx, trachea, and bronchi is usually congested, and the air passages contain a variable quantity of bloody or mucous froth. In persons dying in the water from other causes than asphyxia, these appearances are absent. Foreign substances from the water, such as sand, weeds, etc., or materials regurgitated from the stomach, may find their way into the air passages during the act of drowning or as a post-mortem occurrence. Thus, in bodies washed about the bottom, sand or mud may get into the air passages for a certain distance, from the mechanical action of the water.

The lungs in typical cases are distended so that they fill the thorax and cover the heart. The increased size is due partly to congestion, partly to the presence of the fluid in which the person was drowned, which is often inspired during the act of drowning, and partly to the distention of the air vesicles with air. In cases of drowning in which there is a struggle and water is breathed in, the lungs may contain considerable fluid; but, as a result of decomposition, this may find its way in greater or less quantity into the pleural cavities by transudation, leaving the lungs comparatively empty. It should be remembered, however, that a considerable quantity of reddish fluid may collect in the pleural cavities under other conditions than drowning, through a post-mortem change, by transudation from the blood-vessels and other adjacent tissue.

The Heart.—In those who die from asphyxia the right cavities are usually filled

with fluid blood, while the left cavities are empty. But when death is due to complex causes this may not be the case.

The abdominal viscera may be congested in persons who die from asphyxia.

The Stomach.—The fluid in which the person was drowned, sometimes mixed with sand, weeds, etc., may be swallowed during the act of drowning. On the other

FIG. 297.—SUFFOCATION FROM THE LODGMENT OF A LARGE PIECE OF MEAT IN THE LARYNX. This individual died within a few seconds after bolting this mass of meat.

hand, sand may wash for a short distance into the esophagus in dead bodies washing about the bottom.

In persons dying in the water from syncope, shock, etc., we may find no lesions. When the death is partly due to asphyxia and partly to other causes, the lesions may vary in numerous ways, which need not be described here.

In important cases of doubtful drowning it is desirable carefully to collect and save some of the fluid from the lungs and stomach for microchemical examination, since the identification of these fluids with those in which the person was presumably drowned will often give certainty to an otherwise doubtful case.

For the detailed consideration of the anatomical diagnosis of drowning, the changes which bodies dead from drowning undergo from decomposition, and the factors bearing on the question of suicide, homicide, etc., we refer to works on medical jurisprudence.

Sudden Death.

Some forms of sudden death from violence have been already considered. Aside from these, by sudden death, in the ordinary sense, is usu-

FIG. 298.—ENLARGED THYMUS—SUDDEN DEATH. CHILD TWELVE YEARS OF AGE.
Showing enlarged lymph-nodules at the base of the tongue and in the walls of the pharynx.

ally meant "the rapid and unforeseen termination of a latent acute or chronic disease." We shall not consider here sudden death either from violence or poisoning or in well-defined and evident acute or chronic diseases: it will be practicable only to enumerate some of the more common conditions under which sudden death may occur—and first in the *adult.*

Circulatory System.—Heart—fatty degeneration, chronic myocarditis, abscess of the myocardium, rupture, lesions of the coronary arteries, endocarditis, and pericarditis. Blood-vessels—arteriosclerosis, aneurysms, especially intracranial, intrapericardial, abdominal, and pulmo-

nary; rupture of the aorta, congenital narrowness of the aorta, thrombosis or embolism of the pulmonary or cerebral arteries.

Brain—hemorrhage, meningitis, abscesses, and tumors. Very slight

FIG. 299.—ENLARGED THYMUS.
Case of sudden death in child of twelve years.

injuries of various parts of the body have been followed by sudden death, probably through vagus inhibition. Syncope or shock may terminate in death.

Respiratory System.—Foreign bodies lodging at the entrance to the

larynx are not infrequently followed by immediate death without evidence of asphyxia (Fig. 297). Edema of the glottis, edema of the lungs, hypertrophy of the thyroid, mediastinal tumors, pleurisy, pneumothorax, and pulmonary embolism may lead to sudden death.

Abdominal Viscera.—Rupture of visceral abscesses; perforation of ulcers of the gastrointestinal canal; rupture of the spleen, especially if the latter be enlarged as in malaria or typhoid fever; extrauterine gestation, retrouterine hematocele, and rupture of the uterus, are among the lesions not infrequently leading to sudden death.

Sudden death is frequent in diabetes, in various forms of kidney lesion and in alcoholism, and in association with the so-called lymphatic constitution.[1]

In *young children* sudden death is most often associated with disorders of the respiratory system; they thus differ from adults, in whom lesions of the circulatory system are of the greatest significance. Brouardel attributes sudden death in children usually to one of five principal causes—syncope, convulsions, asphyxia, pulmonary congestion, and intestinal disorders. A large thymus (Fig. 298 and 299) with the lymphatic constitution is frequent in cases of sudden death in young children[2] (see page 500).

[1] See *Ewing*, New York Med. Jour., 1897, lxvi, 37 (bibl.).

[2] For further details on sudden death, consult *Brouardel*, Death and Sudden Death, English translation, 1897; also *Ewing*, in Peterson and Haines' Text-book of Legal Medicine, Philadelphia, 1904.

PART II.

SPECIAL PATHOLOGY.

SPECIAL PATHOLOGY.

General Considerations.

We have now completed the study of those fundamental processes and structural alterations which are embraced in general pathology. These have been considered without reference to special regions or organs of the body. We here enter upon the study of these pathological processes and their associated lesions as they are modified by the special conditions and characteristic structures of one and another of the tissues or organs or regions of the body. It is clear that both the disease processes and the structural alterations with which these are associated may be modified by the functional and structural peculiarities of the affected organ. Thus while degeneration, regeneration, inflammation, etc., may be fundamentally similar, for example, in liver, kidney, and nerve, they may present sufficient variation in one or another of these parts to require a separate consideration and even a special nomenclature. We shall have occasion to call attention now and then to those functional and structural characteristics of the organs which often throw much light upon their mode of response to the various excitants of disease.

It is well, on the other hand, to remember that there are in all the organs and in most parts of the body certain elementary structures, such as connective tissue, blood- and lymph-vessels, and nerves, whose lesions are quite similar wherever they may be. So that many forms of lesion involving these structures, while of varying significance to the organism, differ in the various parts of the body chiefly in distribution or topography.

CHAPTER I.

THE BLOOD AND THE BLOOD-FORMING ORGANS.

The blood may be considered as a fluid intermediary tissue, delimited from other tissues by little more than a layer of endothelial cells. This tissue contains red corpuscles, platelets, and a variety of leucocytes suspended in plasma. Its composition is extraordinarily constant in the normal individual, the only fluctuations being a tidal rise in solid metabolic substances, such as glucose, fat, urea, amino acids, etc., during digestion, and a slight variation in gaseous content between such times when the body is at rest and when it is active. Slight variations in the number of red and white corpuscles also follow the ingestion of food or of large quantities of fluid. In disease of any description the blood is more or less altered, though it is not always possible to detect the changes by any but the most refined methods.

Changes in the Composition and Structure of the Blood.[1]

When the blood clots, the serum is found to contain a large number of ferments and antibodies, either normally present in the plasma or set free from the leucocytes and blood plates.[2]

The Coagulability of the Blood and the characters of the resulting clot vary widely, depending partly upon the composition of the fluid and partly upon the conditions under which the coagulation occurs. There may be very little coagulation of the blood in death from suffocation, or from conditions which interfere with the aeration of the blood and permit the accumulation of carbonic acid within it. Thus, in death from strangulation, high-voltage electric currents, drowning, many chronic diseases, or scurvy, and under many conditions which we do not understand, the blood may remain fluid, or nearly so, after death. On the other hand, in a variety of infectious diseases, such as rheumatism, pneumonia, etc., very voluminous clots may be formed, although this is by no means constantly the case. The fact that large clots form after death is not conclusive evidence that an undue amount of fibrin-forming elements was present in the blood, nor does the absence of marked coagulation prove a diminution in the blood of fibrin-forming elements.

The composition of the clot varies with the rapidity of its formation and with the specific gravity of the plasma. Clots very rapidly formed in plasma of high specific gravity, or in blood still slowly circulating,

[1] A fuller discussion of the subjects in this chapter can be found in *DaCosta*, Clinical Hematology, 3d ed., Philadelphia, 1905; *Naegeli*, Blutkrankheiten und Blutdiagnostik, Leipzig, 1923, and *Wood, F. C.*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917. For an extensive bibl. see *Paltauf, A.*, Krehl and Marchand, Handbuch d. allg. Pathologie, Leipzig, 1913, ii, and the files of the Folia Hæmatologica.

[2] See *Oppenheimer, C.*, Die Fermente und ihre Wirkungen, 4th ed., Leipzig, 1913.

are apt to be dark red, from admixture of red cells and fibrin. After complete failure of circulation, especially in plasma of low specific gravity, the red cells tend to settle to dependent vessels. Yellowish white succulent clots then form in the clear supernatant plasma, while soft black clots result from the excess of red cells collected in the dependent vessels.

The theory of coagulation of the blood is that four substances are necessary for the production of fibrin: fibrinogen, prothrombin, thrombokinase, and calcium salts. By the interaction of the latter three, thrombin is produced; and this substance acting on fibrinogen causes the formation of fibrin, or clotting. The fibrinogen is in solution in the plasma. By the action of thrombin upon it, it is split into a soluble serum globulin and fibrin. Prothrombin is present in the circulating blood and of itself has no action on fibrinogen, but in the presence of thrombokinase and a calcium salt, a new body, thrombin, is formed, which acts upon fibrinogen. Thrombokinase is not found in the plasma, but is present in the tissues and in the leucocytes and blood-platelets. It is possibly a lipoid related to cephalin. In addition, the blood contains an antithrombin which prevents the combination of thrombin and fibrinogen. An antiprothrombin, also, is found in the tissues and may be present in the blood, preventing the conversion of thrombin into prothrombin and thus slowing coagulation.[1]

The time of coagulation of the blood in healthy persons is fairly constant when determined by accurate methods. In disease, considerable variations have been noted in the coagulation time. In cases of hereditary hemophilia the blood may require 60 to 70 minutes to coagulate instead of the normal 7 to 10 minutes. In jaundice the coagulability of the blood may be impaired. Some of the severe anemias and purpuras may also show moderate slowing of coagulation. Repeated hemorrhages shorten the time of coagulation. Transfusion of whole blood or even the injection of serum may shorten the coagulation time and check hemorrhage. Calcium salts seem to have some influence. Intravenous injections of gelatin have some value. Preparations of thrombokinase from fresh tissues or blood platelets are valuable in checking bleeding but are dangerous to inject intravenously.

Reaction of the Blood.—The blood is very slightly alkaline and fluctuates but slightly in reaction under ordinary conditions of living. Excessive exercise may cause the formation of more lactic acid in the muscle tissues than can be rapidly neutralized and hence change the reaction towards the acid side somewhat. A considerable degree of local acidity may, however, occur in the tissues without altering the blood reaction. This may be most easily accomplished by the injection of adrenalin, which causes great vascular constriction.[2] The excretion of large amounts of gastric juice during a meal diminishes the total acid in the organism and slightly shifts the reaction toward the alkaline side,

[1] *Howell, W. H.*, Am. Jour. Physiol., 1914, xxxvi, 1; and Harvey lectures, 1916–17, Philadelphia, p. 272; *Minot, Denny,* and *Davis,* Arch. Int. Med., 1916, xvii, 101; *Hurwitz* and *Drinker,* Jour. Exper. Med., 1915, xxi, 401.

[2] *Drury* and *Rous,* Jour. Exp. Med., 1926, xliii, 669.

but both of these variations are extremely small and are not detectable except by extremely refined methods, nor are they anything but transient. The mechanism for this stabilization of the reaction of the blood is very complicated, being partly mechanical through the respiratory apparatus and partly chemical. The chemical aspect depends upon the presence in the fluid of certain labile substances which have a buffering capacity, in other words, are capable of neutralizing either an excess of acid or alkali. The chief agent in this process, especially of binding carbon dioxide, is the hemoglobin of the red cells. In addition the alkaline phosphates play an important role in which they are assisted by the bicarbonates. At the same time an increase in the rate of respiration removes acid from the blood in the form of carbon dioxide and thus assists the chemical agents in their work of maintaining neutrality. In health the range of reaction is very narrow, being from pH 7.3 to 7.5. The extreme range in disease is from a pH of 7 to 7.8. The higher acidity has been observed in the terminal coma of diabetes while tetany and death occurs when an alkalosis exceeding pH 7.8 occurs. The determination of the true reaction of the blood can be made by comparing the color changes obtained when small quantities of serum are mixed with suitable indicators and contrasted with standard mixtures of the same indicators in solutions of known reaction or by determining by electrical methods the actual hydrogen ion content of the blood. The alkali reserve is often greatly reduced though the reaction of the blood may still remain within normal limits. This fact—of great clinical importance—is easily determined by estimating the combining power of the blood for carbon dioxide. The normal figures are 55 to 65 cc. per 100 cc. of blood. In extreme acidosis this may fall to 25 cc. or less. In alkalosis the amount may rise to 90 cc.

ALKALOSIS.

As a rule, the blood of those suffering from uremia shows an excess of acid, as has been emphasized by Chase and Myers,[1] but where sodium bicarbonate is administered to combat such acidosis an alkalosis may result, especially if the renal function is poor. Clinically, if we except alkaline therapy, alkalosis is most frequently seen in pyloric or upper intestinal obstruction. It has also been observed in rapid breathing from various causes, such as hysterical hyperpnea, cardiac failure and fever. It has been generally believed that alkalosis occurring in intestinal obstruction is dependent on chloride depletion caused by the vomiting. It has been shown, however, experimentally that in intestinal obstruction the fall in plasma chlorides occurs before vomiting begins, so that the alkalosis is not due to loss of the chlorides by vomiting. While vomiting frequently is a cause of alkalosis, it is possible that the hydrochloric acid is used by the body in neutralizing some toxic substance, and this withdrawal of chlorine from the blood leaves an excess of alkali which ordinarily would be rapidly compensated by the excretion of an excess, but in the presence of damaged kidneys, compensation cannot

[1] *Chase* and *Myers*, Jour. Am. Med. Assn., 1920, lxxiv, 641.

take place. This suggestion, however, does not explain why patients with uremia and repeated vomiting do not regularly have alkalosis. Cases of elevated pH may also have a high bicarbonate, whereas, as has been pointed out by Van Slyke,[1] the plasma bicarbonate is not an infallible guide to the pH. The carbon dioxide may be high and the pH normal, or the pH may be increased and the carbon dioxide remain normal. In cases of alkalosis the urine may be acid, especially in the presence of renal insufficiency.[2]

Anhydremia—the condition in which the blood contains an excessive proportion of albumin, cells, and other solid elements—occurs in diseases associated with excessive serous discharges from the intestines. It is extreme in some cases of cholera, and has been noted in a lesser degree in other infectious diseases, as pneumonia and diphtheria.

After removal of large quantities of fluid from the peritoneal or pleural cavities a passing concentration of the blood even to the doubling of the number of red corpuscles present may be observed. This is due to the rapid transudation of serum from the blood to take the place of that withdrawn from the serous cavity. When the balance is again established the anhydremia quickly gives place to the opposite condition, hydremia.

Hydremia is that condition in which the blood contains a large amount of water in proportion to the solid ingredients. It occurs in a variety of diseases of the heart, lungs, liver, and kidneys, and characterizes all forms of anemia.

Hemoglobinemia.—Owing to the destruction of red blood-cells in some forms of poisoning, burning, etc., the blood plasma may contain free hemoglobin, by which it is discolored (*hemoglobinemia*). A hemoglobinemia is produced, also, in healthy persons by the transfusion of blood from an unsuitable donor (see page 535) a similar destruction of the red cells with solution of the hemoglobin is occasionally observed following direct transfusion in persons suffering from severe anemia, especially of the pernicious type.

This free hemoglobin can be easily detected in the serum by the spectroscope. Hemoglobinemia is regularly present in pernicious malaria. It occurs in some of the severe infections with hemolytic organisms and is also seen in the terminal hemorrhagic stage of acute leukemia. The paroxysmal type is of two varieties, one induced by cold, the other by over-exertion. The conditions underlying this form of intravascular hemolysis are still not understood. Whether the corpuscles are defective or a hemolysin is present in the blood is still an unsettled question.

[1] *Van Slyke*, J. Biol. Chem., 1921, xlviii, 153.

[2] For further details see *Harrison* and *Perlzweig*, Jour. Am. Med. Assn., 1925, lxxxiv, 671; *Kast*, *Myers*, and *Schmitz*, ibid., 1924, lxxxii, 1858; *Myers*, *V. C.*, Chemical changes in the blood and their clinical significance, Physiol. Reviews, 1924, iv, 274; *Wilson*, *V. W.*, Neutrality regulations in the body, Physiol. Reviews, 1923, iii, 295. Further consideration of the methods and results cannot be given here. Those interested should consult *Henderson*, Ergebn. d. Physiol. (Asher-Spiro), 1909, viii, 254; *Sellards*, *A.*, Principles of Acidosis, Cambridge, 1917 (bibl.); *Michaelis*, *L.*, Die Wasserstoffionenkonzentration, Berlin, 1914 (bibl.); *Sörenson*, *S. P. L.*, Ergebn. d. Physiol. (Asher-Spiro), 1912, xii, 393; *Van Slyke*, *D. D.*, Physiol. Reviews, 1921, Vol. I; and *Macleod*, *J. J. R.*, Physiology and Biochemistry in Modern Medicine, 5th Ed., St. Louis, 1926.

Unless the setting free of hemoglobin exceeds a certain rate the substance is rapidly changed by the cells of the reticulo-endothelial system into bile, so only if large quantities are set free does the coloring matter appear in the urine (*hematuria*).

Anemia.—In general, anemia means a diminished quantity of blood or of red blood-cells in the vessels of the whole or any part of the body. With one exception—mild chlorosis—it is invariably characterized by a reduction in number and change in form of the red cells (*oligocythemia*), and occasionally by lowered alkalinity and coagulability. It is associated with a reduction in specific gravity, in hemoglobin, and in solid elements. Hydremia and an increased tendency toward osmosis are equally constant features of this condition. The albumins remaining in the serum after coagulation are very slightly diminished in anemia.

Generally speaking, anemia is produced by excessive hematolysis, or by defective hematogenesis, or by actual loss of blood, in bulk (hemorrhage), or in its fluid ingredients (transudation).

Anemia may be secondary to hemorrhage, to exudative processes to prolonged malnutrition, to chronic organic diseases of many kinds, especially of the kidney, to the action of poisons, to congenital hypoplasia of heart and arteries, to functional disturbances of an unknown nature in the blood-forming organs, and to wholly unknown causes. Simple atrophic changes in many tissues, hypertrophy of the red marrow, lymph-nodes, spleen, liver, and thymus, fatty degeneration of the liver, kidneys, heart, and blood-vessels, with capillary hemorrhages and transudations, are frequent accompaniments of severe anemia.

Polycythemia.—By polycythemia in its proper usage is meant an increase in the number of corpuscles in the blood without necessarily an increase in the total volume. This condition is frequently noticed in chronic dyspnea from either congenital or acquired heart disease, in certain chronic diseases of the lungs accompanied by cyanosis, and after poisoning by illuminating gas. What may be termed a physiological polycythemia has been observed in persons living at high altitudes. This has been attributed to the stimulating effect of the diminished oxygen partial pressure on the blood-forming organs, which causes them to produce an excessive number of red cells, and to the rapid evaporation from the skin which takes place, thus concentrating the blood by the transfer of plasma from the blood to the tissues. The question can not, however, be regarded as finally settled.[1] Another form of physiological polycythemia is seen after severe labor and is regularly found in those in athletic training. Whether this increase is simply a hyperplasia of the blood due to the demand for more working material to carry oxygen or to a circulatory readjustment is not yet determined.[2]

The other type of polycythemia, seen in diseases in which the circulation is interfered with, is probably entirely a local phenomenon, the increase in the number of corpuscles being due in all probability to the concentration of the blood-cells in the peripheral capillaries. This is

[1] For a very full discussion of the work of previous observers and many important personal observations, see *Zuntz*, *Löwy*, *Müller*, and *Caspari*, Hohenklima u. Bergwanderungen, Berlin, 1906.

[2] See *Hawk*, *P. B.*, Am. Jour. Physiol., 1904, x, 384; *Lamson*, *P. D.*, Jour. Pharmacol. and Exper. Therap., 1916, ix, 129; *Scott*, *F. H.*, Am. Jour. Physiol., 1917, xliv, 298, 313.

induced by the increased viscosity of the blood incident upon the increased carbon dioxide content following the imperfect aeration in the lungs. The polycythemia disappears in such cases very promptly on inhalation of oxygen, and at the same time the viscosity falls. As soon, however, as the oxygen treatment is terminated the peripheral stasis reappears. In cases of chronic cardiac disease with broken compensation the disappearance of the polycythemia is noted as soon as the heart lesion improves. While the polycythemia is usually a general phenomenon, that is, the blood concentration exists in all the peripheral vessels, it may occasionally be local. The most striking example of such local concentration of the formed elements of the blood is seen in cases of intrathoracic tumor with a compression of the superior vena cava and azygos veins. Under these circumstances intense congestion of the upper extremity may be induced, and blood taken from the finger may show a million more red cells to the cubic millimeter than that taken from the toe.[1]

Plethora.—The existence of a true plethora, that is, an increase in the volume of the blood accompanied by a coordinate increase in corpuscles, has long been debated; but recently cases have been reported, occurring chiefly in persons suffering from a disease of unknown etiology, generally accompanied by hyperplasia of the spleen or bone-marrow, high blood pressure, and cyanosis, and designated clinically as polycythemia or erythremia. In a few instances large solitary tubercles of the spleen have been found. The number of red and white cells and the amount of hemoglobin are greatly increased. The condition of plethora may be suggested at autopsy by the very great distention of all the vessels and the overfilling of the organs with blood.[2] The only accurate method, however, is to determine the total amount of blood in the body during life by a procedure such as Haldane's,[3] by which the patient inspires a measured quantity of carbon monoxide. A sample of the blood is then taken and analyzed to determine what percentage of hemoglobin has been altered into carbon monoxide hemoglobin.[4]

THE RED BLOOD-CELLS.

These may be diminished in number and may undergo various changes in shape and size and structure.

Alteration in Number of the Red Blood-Cells.

Oligocythemia is that condition of the blood in which the number of the red cells is reduced. This reduction in number may be temporary, as after hemorrhage, or it may be persistent, as in some forms of anemia. The number of red blood-cells may in extreme cases of anemia be reduced

[1] For study of polycythemia, with bibl., see *Lucas, W. S.*, Arch. Int. Med., 1912, x, 597; *Senator*, Polyzythämie und Plethora, Berlin, 1911; and *Hirschfeld*, Polyzythämie und Plethora, Halle, 1912.

[2] *Westenhoefer*, Ein Beitrag zur pathologischen Anatomie der plethora vera, Deutsch. med. Wchnschr., 1907, xxxiii, 1446.

[3] *Haldane* and *Smith*, Jour. Physiol., 1897, xxii, 231; 1900, xxv, 331.

[4] For a full review of the subject see monograph by *Weber, F. P.*, Polycythemia, Erythrocytosis and Erythremia, London, 1921.

to one-tenth of the normal, or even less; that is, from the normal number, which is between four and five millions, there may be a reduction to half a million or less.

A persistent diminution in the number of red cells may be effected either by increased destruction (*hematolysis*) or by defective formation of these elements, but the relation of the two factors in the production of the chronic anemias is as yet imperfectly determined.

Excessive hematolysis occurs after burns, is the result of poisoning by arsenic, phosphorus, and chlorates, phenylhydrazin, nitrobenzol, acetanilide, etc., and may occur in infectious diseases through the action of bacterial toxins. All stages of a peculiar destruction of red blood-cells may readily be followed in the blood in malaria. In chronic infectious diseases and in prolonged suppuration, destruction of red cells is probably effected, in part, by toxic agents circulating in the blood. In pernicious anemia the condition of the blood may, with considerable certainty, be referred largely to a destruction of red cells by some unidentified toxic material in the blood.

In the destruction of the red cells, especially if rapid, hemoglobin may separate from the cells, dissolve in the plasma (*hemoglobinemia*), and may then be excreted unchanged in the urine (*hemoglobinuria*). Such destruction occasionally follows chilling of the extremities after exposure to cold in persons suffering from a disease known as paroxysmal hemoglobinuria.[1]

The gradual and more common form of destruction of red cells is attended with an alteration of the hemoglobin, effected chiefly in the liver, and with its deposit in the endothelial and glandular cells of various organs, especially in the liver, spleen, kidneys, and bone-marrow, and secondarily in any of the tissues.

A part of the altered hemoglobin is to be found in the form of pigment granules, or as a diffuse deposit, in the cells of the above-named organs, where its content of iron may or may not be demonstrable by microchemical tests (*hemosiderin*). Another product of the hemoglobin, not containing iron, may be found in the same situations, in the forms of granules or crystals (*hematoidin*). Finally, the derivatives of hemoglobin are excreted largely in the form of normal or pathological urinary pigment. The remaining fragments and stroma of the red cells are soon removed from the circulation largely by leucocytes, and partly by endothelial cells and giant cells, in the liver, spleen, and marrow.

Defective hematogenesis must be regarded as an important factor in the production of such anemias as are associated with pathological changes in the bone-marrow (*pernicious anemia*), and in the lymph-nodes, spleen, and liver (*leukemia*). This, too, is probably the chief cause of the persistence of an anemia following prolonged malnutrition (*secondary anemia*). The pathological changes in the blood-producing organs may sometimes arise as primary diseases of these organs, or similar changes may be secondary to excessive demands for the regeneration of the blood.

[1] For an interesting study of the conditions underlying the hemolysis which occurs in paroxysmal hemoglobinuria, see *Donath* and *Landsteiner*, Ztschr. f. klin. Med., 1906, lviii, 173.

In mild grades of anemia the regeneration of the blood is attended with an hyperplasia of the red marrow, which replaces the yellow marrow of the long bones. The chief defect in the production of red cells may then be a deficiency in hemoglobin (*chlorosis*). In severe and prolonged anemia, under the influence of toxic agents in the blood, the reproduction of cells may be insufficient, and these new cells may be more susceptible to the action of the toxic agent, which is itself the cause of their structural defects. In such cases the normoblasts of the marrow may be produced in very large numbers and form red cells of normal or slightly diminished size, or they may be replaced by very large nucleated red cells (*megaloblasts*); from these are developed very large red cells which are comparatively incapable of the functions of the normal cell. The megaloblastic form of regeneration is confined to the anemia of a pernicious type, with the exception of the form due to the Bothriocephalus latus or that following the prolonged action of certain organic poisons such as nitrobenzol.

Alterations in Morphology of the Red Blood-Cells.

In *mild forms of anemia* the red cells are deficient in hemoglobin, the blood may be pale or watery in appearance, and the cells appear in the fresh condition as very pale discs or as slightly refractive rings inclosing a nearly colorless central mass. In dry preparations stained with eosin, such cells may show only a narrow red ring surrounding a central portion which is entirely devoid of hemoglobin. In this grade of anemia there may be noted moderate differences in size and irregularities in shape of the red cells. In severe anemia and under a variety of conditions, as after certain forms of poisoning, extensive burns, etc., varying numbers of very small red cells are seen, called *microcytes*. They are spheroidal or irregular in shape, and may be excessively minute, and their hemoglobin is either increased, or normal, or diminished. Under similar conditions, red cells are found in a variety of bizarre forms, called *poikilocytes*. In certain forms of anemia very large red cells occur in considerable numbers. These cells, called *megalocytes*, are derived from the large nucleated red cells of the marrow, and their appearance in the blood indicates the early onset or actual establishment of some form of progressive pernicious anemia (see Plate IV, Fig. 4).

Ameboid movement of megalocytes has been observed in specimens from the blood of pernicious anemia examined on a warm stage. The tendency of the red cells to form rouleaux is much diminished or absent in very grave anemia.

Not infrequently a loss of hemoglobin is associated with a change in the stroma of the cell, so that the mass stains slightly with methylene blue. To this change the name of anemic or polychromatophilic degeneration has been given, and it is thought to show a more or less complete coagulation necrosis, by which change the protoplasm of the red cell becomes more basophilic[1] in its staining reaction, though recent investi-

[1] It is convenient to classify the dyes used in staining into the acid, the neutral, and the basic, and to designate cells, in accordance with the relative persistency with which they hold these dyes, as acidophile, neutrophile, or basophile.

gations have shown that similar cells are present in normal bone-marrow and in the blood of the fetus. It is therefore probable that our staining methods do not differentiate between a degenerative change in the body of the cell and a condition expressive of physiological youth. Normally, perhaps, such cells are retained in the marrow until fully developed and appear in the blood only when excessive demands are made upon the blood-forming organs.

Instead of a uniform absorption of the dye some parts of the cell may be condensed in the form of small granules or rings occupying the cell body and staining more deeply with methylene blue than do normal cells (*granular degeneration*).

It should be remembered that during the manipulations required in making dried specimens the red cells may suffer a variety of artificial changes, many of which are very confusing.

Nucleated red blood-cells are found in the blood in all forms of anemia, and their appearance indicates regenerative activity on the part of the blood-producing organs. Their presence in the blood in large numbers, though at all periods of extrauterine life abnormal, has been regarded as of favorable import in disease. Within a few hours after severe hemorrhage nucleated red cells may be noted in considerable numbers.[1] During the regeneration of the blood in anemia, the occurrence of nucleated red cells is nearly constant, but subject to rather sudden periodical variations sometimes called "blood crises." In favorable cases of anemia nucleated red cells of normal size only (*normoblasts*) (Plate IV, Figs. 2 and 3) are seen, whose compact, darkly staining nuclei may be found either in the center of the cell or slightly protruding from the periphery; or, nuclei apparently quite extruded from the cell may be found free in the plasma.

In severe anemia attended with an abnormal type of blood formation, very large nucleated red cells (*megaloblasts*) (Plate IV, Fig. 4) appear in varying numbers. The protoplasm of these cells often shows an excess of hemoglobin, but frequently the purple stain produced by a combination of the eosin and methylene blue indicates an altered form of hemoglobin, or very fine basophile granules may be demonstrated by treatment with methylene blue. The nuclei of the megaloblasts may be single and compact, or a single large nucleus may show stages of direct division, or in extremely large cells (*gigantoblasts*) the nuclei may present phases of mitosis.

THE WHITE BLOOD-CELLS.

The Leucocytes of Normal Blood.

The leucocytes of normal blood may be classified according to their place of origin, or by the character of their nuclei, or by the reaction of the granules in their protoplasm to certain dyes. The most service-

[1] The appearance of nucleated red cells and abnormal forms has been frequently noted in those who have recently arrived in mountainous regions, the probable explanation being that the lowered oxygen tension of the rarefied air demands a larger amount of hemoglobin to supply the wants of the tissues, with the result that for a short time immature red cells are set free from the bone-marrow.

able classification is that based both upon the character of the nucleus and upon the reaction of the protoplasm to dyes, according to which we may distinguish in normal blood the following forms (see Plate IV, Fig. 1):

1. **Lymphocytes,** small leucocytes of about the size of red cells or larger, with a single, compact, deeply staining nucleus, surrounded by a thin rim of homogeneous protoplasm. The cell body usually possesses a stronger basophilic reaction than the nucleus, so that in staining with methylene blue the nucleus shows as a pale spot in the center of the dark ring of the cell body. This ring is often ragged in its outline and may show distinct projections which are sometimes cast off into the circulating blood. Large and small lymphocytes may be distinguished (Plate IV, Fig. 5).

When deeply stained with a methylene azure-eosin mixture, the bodies of a certain number of the lymphocytes show moderate numbers of so-called azure granules. These granules are usually not found in the lymphocytes from normal blood. They have been variously interpreted (a) as granules of the same specific quality as those in other leucocytes, (b) as secretory products of the cell protoplasm occurring during degenerative changes, and, finally, (c) as very small nuclear fragments set free in the protoplasm of the cell. The last view is strongly suggested by morphological appearances in the cells.

2. **Large mononuclear leucocytes,** with a single, compact or vesicular, rather faintly staining nucleus, and a relatively large amount of protoplasm which stains much less strongly than the nucleus. They are probably derived from the reticulo-endothelial tissues. They contain no oxidase ferment but can be vitally stained with neutral red. Some, however, still regard them as precursors of the myelocytes.[1]

3. **Transitional leucocytes,** of the same size as many of the large mononuclear leucocytes, with a compact or vesicular, irregular or incurved nucleus, and a considerable mass of protoplasm, in which fine neutrophile granules can occasionally be demonstrated.

4. **Polynuclear neutrophile leucocytes,** of the same size as the transitional leucocytes, with a partially or completely divided nucleus, of which the separate portions are either compact or vesicular, deeply or faintly staining, and with considerable protoplasm in which distinct granules may be demonstrated by the neutral dyes.

5. **Eosinophile cells,** of the same characters as the ordinary polynuclear leucocytes, but containing in their bodies large refractive granules, which stain deeply with so-called acid dyes such as eosin.

6. **Basophile cells,** of about the same size as the polynuclear cells, but containing coarse granulations stained only by basic dyes such as methylene blue. The nucleus is small, stains feebly, and is usually lobular. It is often covered very largely by the granulations.

These various forms of leucocytes occur in normal blood in the following proportions, which represent averages only and are subject to considerable variations:

[1] For a full discussion of this much debated question see *Merklen* and *Wolf*, Le Monocyte, Annales d'Anat. Path., 1927, iv, 621.

Polynuclear neutrophile leucocytes	60 to 72 per cent.
Large mononuclear and transition forms	2 to 4 per cent.
Lymphocytes	22 to 35 per cent.
Eosinophiles	2 to 4 per cent.
Basophile cells less than	0.5 per cent.

In the normal blood of young children the relative proportion of mononuclear cells is considerably greater than in that of adults.[1]

The numbers and proportions of the polynuclear leucocytes are in disease subject to very wide variations, and abnormal forms of the white cells frequently make their appearance in the blood.

The Leucocytes of Abnormal Blood.

1. **Myelocytes.**—In many diseases, especially the leukemias but also in acute infections, large mononuclear cells make their appearance in the blood. They measure from 15 to 20 μ in diameter. (Plate IV, Fig. 6.) Three types may be differentiated by the tinctorial relations of their granules: neutrophilic, eosinophilic, and basophilic. The nucleus is usually pale, and oval or round, and lies to one side of the cell. The protoplasm is generally fairly abundant. The neutrophile myelocytes contain large numbers of fine neutrophile granules which, however, often show a basophilic habit when compared with the neutrophile granules of normal blood.

Eosinophile myelocytes are of much the same type, but are easily differentiated by the large size of the granules. The cells are very easily destroyed in the process of making smears, and the granules may be scattered to a considerable distance from the nucleus.

Basophile myelocytes are quite rare, are usually smaller than the other two types, and contain large numbers of irregularly shaped basophile granules.

All these types of cells arise normally from the bone-marrow and can be found in smears from this organ. In advanced leukemias it is probable that the liver and spleen assume to a certain extent their embryonic function and act as centers for the production of these cells.

Myelocytes are found in the blood chiefly in leukemias, but the neutrophile form occasionally appears in severe infectious diseases and in primary or secondary tumors of the bone-marrow. Eosinophile myelocytes have been very rarely seen in high eosinophilia due to the presence of parasites in the body.

2. **Large Lymphocytes.**—While cells of a lymphocytic type appear in normal blood in moderate numbers, a very large cell giving the same staining reactions also occurs in acute lymphatic leukemia. Until recently these cells were considered as unquestionably large types of lymphocytes; but the demonstration of proteolytic and lipolytic ferments by Longcope[2] and of oxidases by Schultze[3] suggests that the cells belong to the bone-marrow group, and not to the true lymphocytes, which

[1] See *Schloss, O. M.*, Arch. Int. Med., 1910, vi, 638.
[2] *Longcope* and *Donhauser*, Jour. Exper. Med., 1908, x, 618.
[3] *Schultze, W. H.*, München. med. Wchnschr., 1909, lvi, 167.

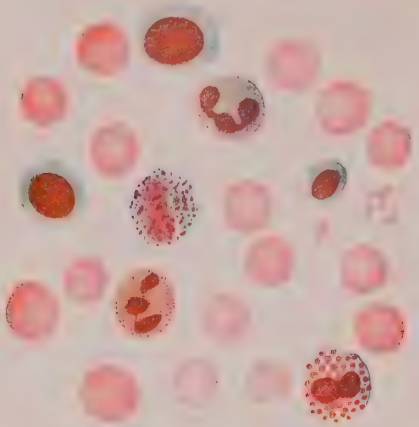


Fig. 1. Normal Blood.

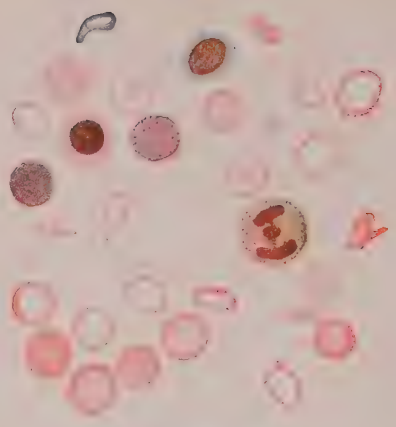


Fig. 2. Chlorosis.

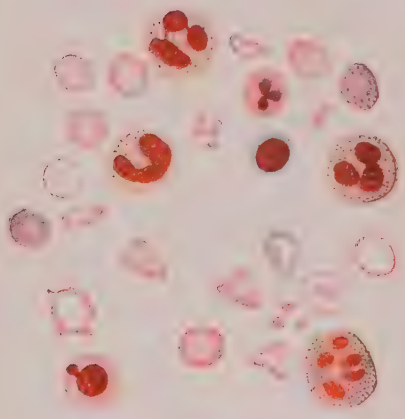


Fig. 3. Secondary Anemia.

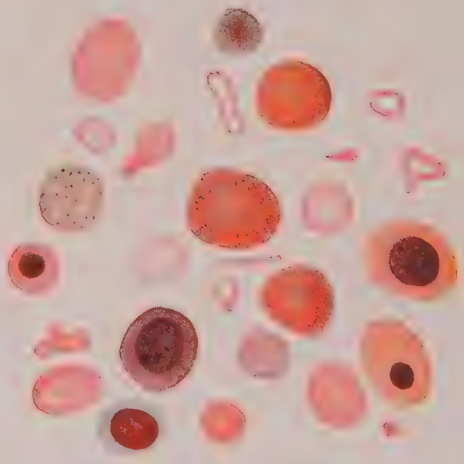


Fig. 4. Pernicious Anemia.

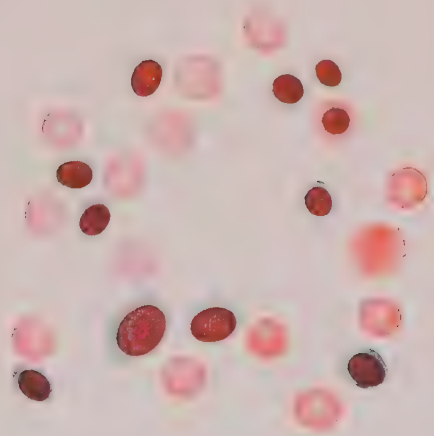


Fig. 5. Chronic lymphatic Leucemia.

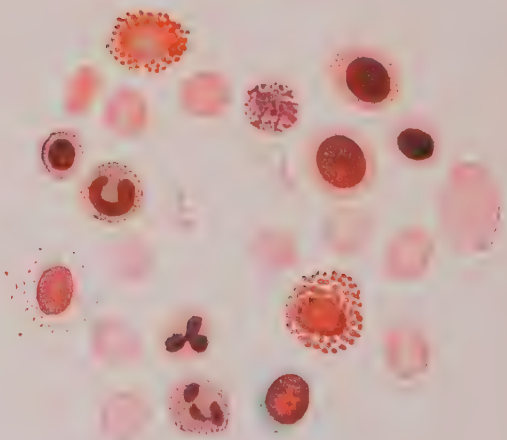


Fig. 6. Myelogenous Leucemia.

Changes in the Morphology of the Blood.

Drawn by Francis Carter Wood. (Magnified 900 Diameters)

Description of Plate IV.

All the Specimens are Stained with Eosin and Methylene-azure.

Fig. 1. Normal Blood.—The red cells are nearly uniform in size and shape. The hemoglobin is fairly evenly distributed, but is slightly more dense near the periphery than at the center, especially in those cells which have dried slowly. In rapidly dried red cells the stain is even throughout. To the left is a lymphocyte with reddish, deeply stained nucleus and a pale bluish cell body, which is narrow in proportion to the size of the nucleus. To the right is a small lymphocyte, smaller than the red cells which surround it, with a deeply stained nucleus and a narrow cell body from which projects a small mass of protoplasm. At the upper portion of the figure is a large oval cell which corresponds to the large mononuclear cell of Ehrlich, but is considered by many equivalent to a large lymphocyte. In the center of the drawing is a cell with a lobed nucleus and purplish granules by which this basophile cell is distinguished from the neutrophile just below it and from the eosinophile in the right lower quadrant. Two neutrophile cells are shown, one with abundant fine granules, the other showing a smaller number; both types being abundantly present in normal blood. To the right is a small cluster of blood-plates, some of which show darker staining masses near the center which are presumed by some observers to be nuclear remains, by others to be fragments of hemoglobin. The eosinophile cell in the lower right-hand quadrant is distinguished from the neutrophile by the coarseness of its granules, which are shot-like and quite regular in form, though not all the granules are of the same size. They often take a much more brilliant red color than the neutrophiles.

Fig. 2. Chlorosis.—The blood was obtained from a young woman of twenty-two years, who had 3,000,000 red cells and 30 per cent. of hemoglobin. The red cells are about of the same size as those in normal blood, but show a greatly diminished amount of hemoglobin to the individual cell, as evidenced by the much fainter staining of a number of cells in the plate which appear merely as remnants. Some of the cells have assumed irregular shapes and are known as poikilocytes. In the left upper quadrant are three forms which may be considered as pathological in circulating blood. Below, to the left, is a purplish red cell rather deeply stained, showing polychromatophilia. To the right of this cell and separated from it by a nucleated red cell of normoblastic type is a cell showing granular degeneration.

Fig. 3. Secondary Anemia.—The blood was obtained from a case of carcinoma of the stomach in which the red cells were reduced to 1,500,000; the hemoglobin was 25 per cent.; the leucocytes, 30,000. The changes in the red cells are much the same as those noted in the chlorotic type. There is marked diminution of the hemoglobin of the red cells with poikilocytosis and also granular degeneration and polychromatophilia. Two nucleated red cells are present, one in the upper right, the other in the lower left-hand quadrant. Both show degenerative changes in the nuclei, which should not be mistaken for mitotic figures. In secondary anemia of this type the polynuclear neutrophiles are notably increased.

Fig. 4. Pernicious Anemia.—The blood was obtained from a case showing 400,000 red cells, 10 per cent. of hemoglobin, and 3,000 leucocytes. The striking features of the blood in this disease are the marked alterations in size, shape, and staining properties of the red cells. The leucocytes are usually diminished in number and show no characteristic changes, with the exception of a relative increase in the lymphocytes. The various types of deformation of the red cells are very well noted in the various poikilocytes in the sketch, some of which contain large quantities of hemoglobin, others a diminished amount. In the red cells approaching more nearly to the normal form it will be immediately noted that the amount of hemoglobin present as evidenced by the depth of stain is relatively large. The cell in the center of the field, for example, stains a great deal more deeply than any normal cell. These deeply staining cells are also very large and often of peculiar oval and irregular form. The so-called megaloblasts are abundantly present in the blood of pernicious anemia, in contrast to the microcytic type of cell usually found in the secondary anemias and in chlorosis. It is this macrocytosis with the consequent increase in the hemoglobin content of each cell that gives rise to the high relative hemoglobin index of the blood of pernicious anemia. A normal-size cell showing marked polychromatophilia is seen above; a macrocyte with granular degeneration is seen below it, and a normal-size red cell with nucleus, or normoblast. In the lower left quadrant is a large erythrocyte with a large nucleus with fine chromatin network. The cell body takes on a combination of the blue and pink of the stain; in other words is polychromatophilic. Below it is a normal lymphocyte. In the lower right quadrant are two other megaloblasts showing a slightly different morphology and with an orthochromatic protoplasm; that is, the cell body takes the eosin alone. The upper cell shows a dense nucleus with thick strands of chromatin forming a network. In the lower the chromatin shows no structure.

Fig. 5. Chronic Lymphatic Leukemia.—The blood of this case showed 3,500,000 red cells, 160,000 leucocytes, and 50 per cent. of hemoglobin. Of the leucocytes 95 per cent. were lymphocytes. It will be noted from the drawing that the red cells are practically normal in size and shape. The abundance and variety of the lymphocytes will be noted immediately. In the upper right quadrant is a single normoblast; in the lower right quadrant of the upper part is a washed-out cell with irregular outline which is a degenerated lymphocyte. In the acute forms of lymphatic leukemia these cells become exceedingly abundant.

Fig. 6. Myelogenous Leukemia.—The blood of this case showed 1,000,000 red cells, 20 per cent. hemoglobin, and 1,200,000 leucocytes, the exact proportions of which could not be determined on account of the large number of irregular and degenerated forms, but myelocytes and basophiles were very abundant. In the upper left quadrant can be seen an eosinophile myelocyte with a single oval nucleus and large shot-like granules. Below it are a normoblast with granular degeneration of the protoplasm and a polymorphonuclear neutrophile with fine granules. In the lower left quadrant can be seen a large degenerated neutrophile myelocyte in which the granules have become scattered over the slide in the process of spreading the blood. To the right and below the center are a normoblast with clover-leaf nucleus, a polymorphonuclear neutrophile and a lymphocyte, and above an eosinophile myelocyte. In the upper right quadrant, beginning at the left, can be seen a small basophile cell with faintly staining nucleus, to the right two myelocytes, one with deeply staining nucleus, the other somewhat fainter, both containing neutrophile granules. To the right a normoblast with pyknotic nucleus, and still farther to the right a so-called basket-cell or degenerated leucocyte.

do not give these reactions. A further discussion of this question will be found under acute lymphatic leukemia (page 542).

3. **Plasma Cells.**—In severe anemias and leukemias and in certain of the infectious diseases, large cells measuring 6 to 15 μ, with a single pale nucleus and a cell body staining very deeply with methylene blue, appear in the circulation. The cell body shows a definite spongy structure. These were named by Türk[1] "irritation forms." It has been shown that these cells have many tinctorial relations with the cells seen in large numbers in chronic inflammations occurring in connective tissue, and though there are slight morphological differences between the two forms yet these blood cells are usually considered as of the plasma-cell group.

4. **Myeloblasts.**—In myelogenous leukemia and also in typhoid fever, large cells resembling myelocytes appear in the circulation, but they contain no characteristic granules stainable either with the Jenner or any one of the azure stains. They can be differentiated from the large mononuclears by the fact that the nucleus is very rich in chromatin and shows large nucleoli. The protoplasm also is more basophilic than that of the large lymphocytes. These cells have been named myeloblasts by Naegeli.

Leucocytosis.

Leucocytosis is that condition of the blood in which the leucocytes are temporarily or persistently increased in number. When several forms of leucocytes are increased in number and the usual proportions are but partially disturbed, we speak of *mixed leucocytosis*. Such a condition is seen in some forms of anemia. When the polynuclear neutrophile leucocytes alone are increased, the condition is termed *polynuclear leucocytosis*, or simply *leucocytosis*. If the mononuclear cells are chiefly affected, the condition may be denoted as *lymphocytosis*. The eosinophile cells alone may be increased.

Polynuclear leucocytosis may be either physiological or pathological.

Physiological polynuclear leucocytosis is seen during normal digestion, in the later months of pregnancy, and in the first days of infancy, and is usually of moderate grade.

Pathological polynuclear leucocytosis occurs in many inflammatory and infectious diseases, and accompanies the various cachexias. Of the infectious diseases attended with leucocytosis may be mentioned pneumonia, diphtheria, scarlet fever, erysipelas, rheumatism, suppurative cerebrospinal meningitis, and any disease associated with a pronounced exudative or suppurative lesion. On the other hand, leucocytosis is absent in uncomplicated typhoid fever, typhus, malaria, measles, influenza, and tuberculosis.

The origin and significance of the leucocytosis of infectious diseases are imperfectly understood, but may be partially explained by the principles of chemotaxis and phagocytosis. From experimental evidence and

[1] *Türk*, Vorlesungen über klinische Hämatologie, Wien, 1904.

clinical observation it is known that during the onset of some infectious diseases the entrance of bacteria or their products into the blood is followed by a disappearance from the circulation of many polynuclear leucocytes, which are removed from the larger vessels and lodged in the capillaries, principally in the lungs and liver. This condition of the blood, called *hypoleucocytosis*, may be attended with a transient reduction in temperature and weakening of the heart's action, and is usually succeeded shortly by the reappearance of polynuclear leucocytes in large numbers, and by a rise of temperature. These leucocytes are apt to gather in regions in which microorganisms are abundant, and are believed to take up and destroy microorganisms (*phagocytosis*), and to prevent their further entrance, and possibly the entrance of their products also, into the circulation. Of the place and method of origin of these new leucocytes very little is definitely known.

In many very severe cases of infectious disease, such as pneumonia, diphtheria, and peritonitis, the initial hypoleucocytosis persists, in which event the disease usually runs an asthenic and fatal course, with a tendency to low temperature and feeble pulse.

The degree of the leucocytosis varies with the extent of the local lesion and the height of the fever associated with the infectious process. In general, leucocytosis may be regarded as the effort of the blood-producing organs to protect the body against microorganisms and circulating toxins. When the peripheral leucocytes are reduced by exposure to radioactive substances or *x*-rays, the body becomes susceptible to microbic invasions and unable to manufacture antibodies[1] (see also page 207).

The blood in typhoid fever presents a peculiar variation from that in most infectious diseases. In the first weeks of the disease there is usually a reduction in the number of leucocytes, especially of the polynuclear forms. In the later weeks the lymphocytes may form 80 per cent. of the leucocytes present in the blood. Each relapse is attended with an increase of the lymphocytosis, while an increase of polynuclear leucocytes usually occurs with complications only.

In the various forms of tuberculosis there is no leucocytosis unless the lesion is markedly exudative in character, as in tuberculous meningitis, or is complicated by suppuration or chronic anemia. In pulmonary tuberculosis with secondary infection by pyogenic cocci, leucocytosis is apt to develop.

Cachectic leucocytosis is a feature of altered conditions of the blood, such as are associated with the growth of malignant tumors, and with many diseases producing secondary anemia. This increase of polynuclear leucocytes may serve to distinguish many forms of secondary from primary anemia. The inflammation and toxemia accompanying many new growths afford a sufficient reason for the appearance of cachectic leucocytosis, but under many other circumstances its direct cause is less apparent.[2]

[1] *Camp, W. E.*, and *Baumgartner, E. A.*, Jour. Exper. Med., 1915, xxii, 174.

[2] For further data concerning leucocytosis, consult *Rieder*, Beiträge zur Kenntniss d. Leukocytose, Leipzig, 1892; *Türk*, Klinische Untersuchungen u. d. Verhalten des Blutes, Wien, 1898.

Hypoleucocytosis occurs not only in infectious diseases, when the polynuclear cells alone are reduced in numbers, but also from shock, reduction of body temperature, and exhaustion, when all forms of leucocytes may be diminished. It is a fairly constant feature of primary pernicious anemia[1] and of influenza.

Polynuclear Eosinophile Leucocytosis is found in a number of unrelated conditions. In bronchial asthma the eosinophile cells are considerably increased, often forming 10 to 20 per cent. of the total white cells. A considerable increase is seen in scarlatina. In acute and chronic diseases of the skin, such as pemphigus, prurigo, and psoriasis, the eosinophiles are often increased to a marked degree, but the condition is not constant. In trichinosis and helminthiasis the increase is so constant that it becomes of diagnostic value in these conditions. A post-febrile eosinophilia is frequently observed.

Lymphocytosis, frequently seen in the anemias, in pertussis, and the acute intestinal disorders of childhood, has also been noted in some forms of secondary anemia (syphilis), and in an extreme degree as the chief characteristic of the blood of lymphatic leukemia. It is also fairly frequent in exophthalmic goiter.

Degenerative Changes in the Leucocytes are usually indicated by variations in the percentage of normal and abnormal varieties, rather than by alterations in the individual cells, for degenerating leucocytes are usually quickly removed from the circulation. Occasionally, however, there may be seen in normal blood a cell in which the nuclear chromatin has entirely lost its power to take the stain; and these degenerating or basket cells are sometimes very abundant in the leukemias. Staining reactions of the various granules, by which degenerative changes may be recognized, have not yet been devised. In leukemia, pernicious anemia, and diphtheria, a diminished reaction to nuclear dyes has been observed. In leukemia, and in the severe infectious diseases, the leucocytes may be extremely cohesive, and it is believed that a large quantity of bacteria or toxins in the circulation may even effect a complete solution and destruction of leucocytes (*leucocytolysis*). Fatty and glycogenic degeneration of leucocytes has been demonstrated.

Blood-Plates.—These are small spherical or oval, transparent bodies which appear in the blood plasma in large numbers. They measure from 2 to 3.5 μ in diameter, though occasionally in pneumonia and suppurative conditions very large plates may be found measuring up to 5 or 6 μ. Structurally they are composed of a peripheral hyaline transparent layer with a granular central mass which is not sharply outlined. This granular mass takes a faint color with the ordinary chromatin stains; the periphery is clear. In stained specimens it is occasionally possible to find long curved protoplasmic processes, simulating cilia, given off from the periphery of the blood plate. Under suitable conditions the blood-plates show ameboid motion.

[1] For hypoleucocytosis, consult *Löwit*, Studien über Physiol. und Pathol. d. Blutes u. d. Lymphe Jena, 1892; *Ewing*, New York Med. Jour., 1895, lxi, 257.

Their number in the blood varies; the average number is considered as approximately 200,000 to 350,000. The number of blood-plates is increased in many anemias, both primary and secondary, and especially in carcinoma. In pneumonia, septic processes, and leukemia there is also an increased number of blood-plates. A diminution of the plates is noted chiefly in cases of purpura and pernicious anemia.

After prolonged exhibition of benzol to leukemic patients, purpuric symptoms may develop, and even fatal hemorrhage. The blood-platelets may be greatly diminished in number, and a fatal termination is certain unless the administration of benzol is stopped. If this is done,

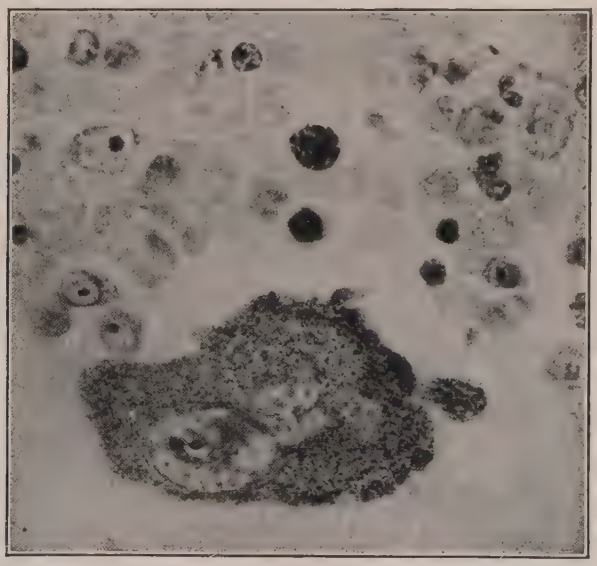


Fig. 300.—Megakaryocytes from Bone-marrow. Showing Formation of Blood-Platelets. From preparation of Dr. J. H. Wright.

the platelets return to normal unless the leucotoxic action of the benzol has gone too far.[1]

The blood-plates are closely connected with the formation of thrombi, and some of the small, so-called white thrombi are entirely composed of these bodies. They are also thought to carry the thromboplastin which plays an important rôle in blood coagulation.

It is now generally accepted that blood-plates are formed from the megakaryocytes of the bone-marrow.[2] These cells frequently show budding masses of the same structure as the blood-plates (see Fig. 300 and 301). The hyaline peripheral zone of the giant cell has the power of ameboid motion and can be observed on the warm stage to give out protoplasmic processes. In addition the blood-plates are found only in

[1] See, for a study of benzol anemia, *Hurwitz* and *Drinker*, Jour. Exper. Med., 1915, xxi, 401.
[2] *Wright*, Jour. Morphology, 1910, xxi., 2; and *Ogata*, Zieglers Beitr., 1912, lii, 192.

such mammalia as have megakaryocytes in the bone-marrow, and it has been noted that blood-plates appear only in embryonal mammalian blood at the time when the giant cells are present in the blood-forming organs.

However, under certain conditions of excessive demand for their formation, the transitional leucocytes, representing the persistent form of the embryonic premegakaryocyte, and the hyperplastic endothelial cells of the marrow may also give rise to the blood-plates.[1]

THE RETICULO-ENDOTHELIAL SYSTEM.

It has been known for many years that if suspensions of discrete particles, such as India ink, are injected into the blood vessels or the peritoneum, these particles are promptly phagocyted and deposited in various organs. Kupffer a generation ago showed this to be true of the

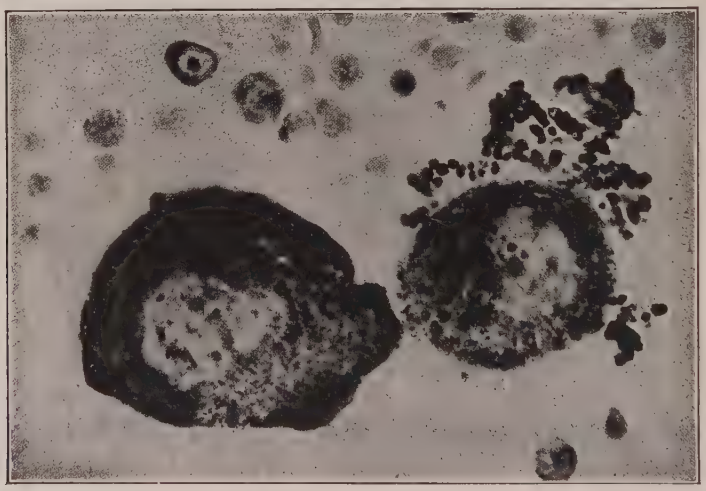


FIG. 301.—MEGAKARYOCYTES FROM BONE-MARROW. SHOWING FORMATION OF BLOOD PLATELETS. From preparation of Dr. J. H. Wright.

stellate cells of the sinusoids of the liver (Fig. 302). In recent years a great deal of attention has been devoted to the investigation of this phagocytic group of cells, all possessing the same biological qualities, and in 1913 Aschoff[2] and Landau introduced the term reticulo-endothelial system to designate the phagocytic cells of the splenic pulp, the cortical nodules and pulp cords of the lymphoid apparatus, the reticulo-endothelial cells of the sinuses of the lymph node, the blood sinuses of the spleen, the sinusoids of the liver, the capillaries of the bone marrow, the adrenal medulla and hypophysis. This grouping was based upon the uniform storage of granules, the size of the stored granules, and the relative avidity of the cells for dyestuffs, either colloidal or in solution. In addition, the classification included the common function of the cells in

[1] *Brown, W. H.*, Jour. Exper. Med., 1913, xviii, 278.

[2] *Aschoff*, The Reticulo-endothelial System, Ergebn. d. inn. Med. und Klindhlk., 1924, xxii, 246, Lectures on Pathology, 1924, Paul Hoeber, N. Y.

producing reticulum and lining sinusoidal, blood and lymph spaces. While almost every type of cell can occasionally engulf coarse foreign particles, the intensity and frequenty of such capacity is a determining factor in this connection. Entirely different relations may be manifested with substances in solution, for example, carmine granules are readily taken up by leucocytes, but carmine in solution is never absorbed by these free-swimming cells. It seems probable also that the cells of the reticulo-endothelial system may under certain conditions become the mobile cells or histiocytes of the connective tissue, and are identical

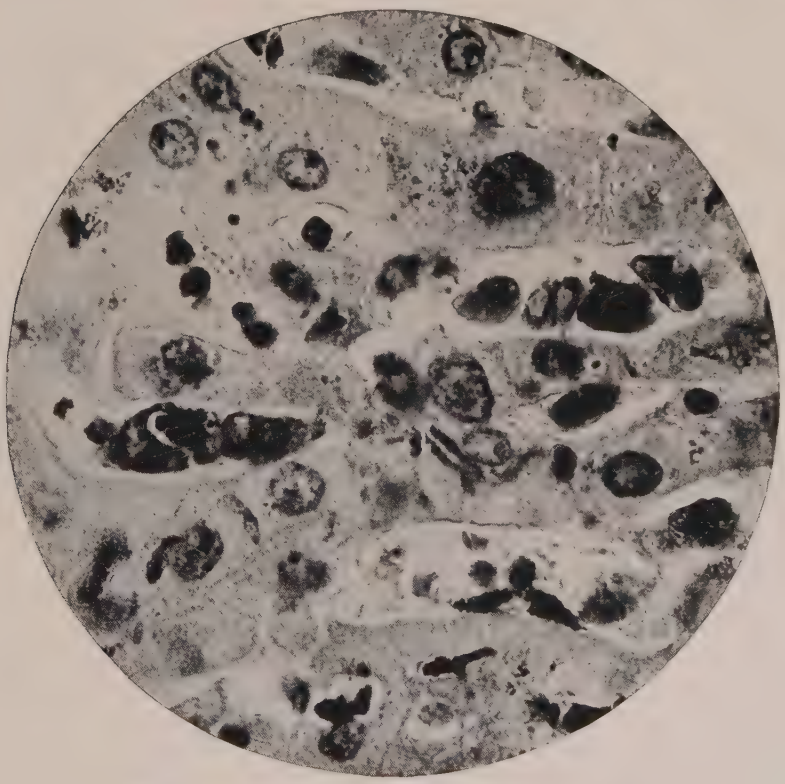


FIG. 302.—PHAGOCYTOSIS OF BILE PIGMENT IN THE KUPFFER CELLS OF THE LIVER IN A CASE OF OBSTRUCTIVE JAUNDICE. × 800.

with the clasmatocytes of Ranvier, the adventitia cells of Marchand, the macrophages of Metchnikoff, the pyrrol cells of Goldmann and the polyblasts of Maximow. The monocytes or mononuclears of the blood stream seem to be related to this group, and when the histiocytes are altered by inflammatory processes such as in typhoid fever, they become the endothelial leucocytes described years ago by Mallory. Kiyono,[1] who made a careful histological study of the cells capable of storing lithium

[1] *Kiyono*, Die Vitalkarminspeicherung, 1914.

carmine, gave the name histiocytes to the reticulo-endothelial cells, and also to certain mobile cells of the blood and the connective tissue. While the monocytes of the blood phagocyte carmine, the lymphocyte does not, though the transformation of the lymphocyte into the histiocyte is not impossible, although Aschoff denies it. Maximow,[1] on the other hand, pictures a very intimate relationship between lymphocytes and the various wandering and fixed phagocytic cells, with a ready transition, either directly or indirectly, from one into the other, and even, through his polyblast, eventually into connective tissue. True endothelium, he holds, is a very fixed type that does not form the mobile, phagocyting, histiocytic elements under discussion.

Foot,[2] using colloidal carbon (Higgin's India ink) which he considers specific for sessile endothelium, not alone for "specific endothelia" of the blood and lymph sinuses, upholds Mallory's conception of derivation of these wandering cells from endothelium in the broader sense, particularly in inflammatory conditions. This author suggests the term "endothelial phagocyte."

Sabin, Doan and Cunningham[3] from a study of the living cells of the chick embryo, the depleted bone marrow of pigeons and rabbits, and from tuberculous lesions conclude that the clasmatocyte is a derivative of the true endothelium, while from the reticulum cells comes a primitive cell type that gives rise to the monocytes (as well as polymorphous leucocytes and lymphocytes). They used a "supravital technique" which consists of applying very dilute neutral red and Janus green dyes to the living cells in cover glass preparation.

Lewis[4] objects to this dual origin because he has observed in hanging drop blood cultures the transformation of monocytes into clasmatocytes, epithelioid cells and giant cells of the Langhans type. The giant cells supposedly characteristic of tuberculosis were seen in both normal and inflammatory tissues. That fibroblasts may be so formed he denies.

Based upon an observation that cells loaded with colloidal iron failed to take up injected dyes the idea of an "endothelial block" originated. That the cells can take up but one substance at one time is refuted by the experience of various investigators, and Aschoff holds that such a blockage could only be very temporary. Nevertheless attempts were made to study the influence of the reticulo-endothelial system upon the formation of antibodies by this method of "block." The results have been contradictory.[5] Gay and Clark[6] found marked decrease in hemolysis and precipitin formation. Jungeblut and Berlot[7] noticed delayed formation of antitoxin, while Standenath believed the precipitin formation increased.

[1] *Maximow*, Physiol. Reviews, 1924, iv, 533.

[2] *Foot, N. C.*, The Endothelial Phagocyte. A critical review, Anat. Rec., 1925, xxx, 15.

[3] *Sabin, Doan* and *Cunningham*, Contrib. to Embry, No. 82, Pub. 361, Carnegie Inst., Washington, D. C., 1925.

[4] *Lewis, W. H.*, Transformation of Mononuclear Blood Cells into Macrophages, Epithelioid Cells and Giant Cells, Harvey Lect., 1925–26, Williams & Wilkins, Baltimore, 1927.

[5] *Boerner-Patzelt, D., Gödel, A.*, and *Standenath, F.*, Das Retikuloendothel, Georg Thieme, Leipzig, 1925.

[6] *Gay* and *Clark*, Jour. Am. Med. Assn., 1924, lxxxiii, 1296.

[7] *Jungeblut* and *Berlot*, Jour. Exp. Med., 1926, xliii, 613, 797.

Lewis and Loomis[1] found enormously increased formation of hemolysins in tuberculous as well as dye treated animals, but the infection must be of suitable severity and not overwhelming. The taking of heterologous skin grafts is said to be favored by a preliminary blocking of the reticulum as if this formed antibodies, which prevented healing. There are a great many references in the literature to similar contradictions.

Simpson[2] showed a marked stimulation of macrophages in the circulating blood from the right heart after injection of various colloids, these cells occurring in showers. Gye and Purdy[3] produced various modifications in sessile cells of the reticulo-endothelial group by injection of colloidal silica, some of them closely resembling those of Gaucher's disease. Elvidge[4] secured red blood cell "crises" and very severe anemia with fine quartz suspensions, as well as with India ink, while Muller[5] produced similar reactions and showed that the protective colloid of the ink was more active than whole ink.

The response of the reticulo-endothelial system to injected substances, Standenath thinks, depends upon 1. Chemical nature, whether acid, neutral, or alkaline (in this relation it must be remembered that neutral colloids are relatively negative in alkaline solution, and relatively positive in acid). 2. Degree of dispersion of colloid. 3. Atrium of administration. 4. Diffusibility. 5. Finally upon the existing functional condition of the storage cell. One might add also the species of animal.

Just as we have a long list of colloidal or particulate substances causing changes, tuberculosis is interpreted as a disease of the mononuclear cells by Cunningham and Sabin.[6] Gödel thinks that we may now speak of a pathological anatomy of the reticulo-endothelial system. Gaucher's disease is a diffuse hyperplasia correlated with a faulty metabolism of the phospholipoids. Primary hemangioendothelioma of the liver, endothelial sarcoma of the spleen, and reticulo-endothelial neoplasms of the lymph nodes are spoken of. Of the infectious diseases leprosy, rhinoscleroma, kala azar, as well as the proliferation in typhoid fever may be mentioned. Monocytic, splenocytic or "stem cell" leukemias are referred to in certain acute cases in which the cells seem to belong to the primitive forms. There is a disease characterized by acute pharyngeal inflammation with general lymph node swelling, enlargement of the spleen and liver, and a monocytosis as high as 78 per cent., which is spoken of as monocytic angina. Even the xanthomatous tumors are now classified with the diseases of the reticulo-endothelial system as representing a pathological phase of the metabolism of the cholesterol esters. Physiologically the reticulo-endothelial system is looked upon as important in the removal of foreign bodies, damaged cells, bacteria or particulate matter from the body, in the resorption and transportation

[1] *Lewis, Paul,* and *Loomis, Dorothy,* Jour. Exp. Med., 1926, xliii, 263.
[2] *Simpson,* Jour. Med. Res., 1922, xliii, 77.
[3] *Gye* and *Purdy,* Brit. Jour. Exp. Path., 1924, v, 238.
[4] *Elvidge,* Jour. Path. and Bacteriol., 1926, xxix, 323.
[5] *Muller, G. L.,* Jour. Exp. Med., 1927, xlv, 399.
[6] *Cunningham, Sabin, Sugiyama* and *Kindwell,* Johns Hopkins Hosp. Bull., 1925, xxxvii, 231. For a general review see *Oberling,* Ann. d'Anat. Path., 1924, i, 87.

of fat, possibly as an extrahepatic place of formation of bile, and as a storage place of water and of many highly soluble substances, such as glucose and salt, but many of these conclusions are still awaiting final confirmation.

METHODS OF EXAMINATION OF THE BLOOD.

Blood may be examined fresh on the warm stage, a method especially useful in studying living parasites. For most purposes, however, it is fixed either before or after spreading in a thin layer on the slide.[1]

BLOOD GROUPING.

The agglutination of red blood corpuscles in man, which may occur when the corpuscles are suspended in serum from another individual, was first described in 1900.[2]

While in the blood of animals no such grouping is demonstrable, Landsteiner[3] found that human bloods could be classified into three groups, while Janský[4] in 1907 pointed out that there was a fourth group. His paper appeared in a language few pathologists read and though followed by a résumé in French was not noticed. Shortly afterwards Moss[5] and others called attention to the four main types and classified them as to their statistical frequency. Moss' classification designated Janský group as group IV. The Janský grouping has been generally adopted on a priority basis. It is as follows:

Janský's Classification

	Serum of Groups			
Cells of Groups	I	II	III	IV
I	−	−	−	−
II	+	−	+	−
III	+	+	−	−
IV	+	+	+	−
	Cells of Groups			
Serum of Groups	I	II	III	IV
I	−	+	+	+
II	−	−	+	+
III	−	+	−	+
IV	−	−	−	−

The proportional distribution of their occurrence in the white population of Europe and America is in round numbers as follows: Group I, 43 per cent.; Group II, 41 per cent.; Group III, 10 per cent., Group IV, 6 per cent. In the American negro the proportions are: Group I, 49 per cent.; Group II, 27 per cent.; Group III, 18 per cent.; Group IV, 6 per cent.

[1] For various methods of fixing and staining the blood see *Weidenreich*, Folia haematologica, 1906, iii, 1; *Schridde* and *Naegeli*, Hämatologische Technik, Jena, 1910; *Wood*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917; *Mallory* and *Wright*, Pathological Technique, 8th ed., Philadelphia, 1924; also see under Malaria, p. 349.

[2] *Greenbaum:* Brit. M. J., 1900, 1, 1089. *Shattuck:* J. Path. & Bacteriol., 1900, vi, 303.

[3] *Landsteiner:* Wien. klin. Wchnschr., 1901, xiv, 1132.

[4] *Janský:* Sbornik Klinický, 1907, viii, 85.

[5] *Moss, W. L.*, Bull. Johns Hopkins Hosp., 1910, xxi, 63; ibid., Jour. Am. Med. Assn., 1917, lxviii, 1905; St. Luke's Hospital Technique, New York, 1922, 2d ed., *Brem, W. V.*, Jour. Amer. Med. Assn., 1916, lxvii, 190; *Ottenberg, R.*, and *Kaliski, D. J.*, Jour. Am. Med. Assn., 1913, lxi, 2138; *Karsner, H. T.*, Jour. Am. Med. Assn., 1918, lxx, 769. For a general survey of the subject of transfusion, see *Bermheim*, Blood Transfusion, Philadelphia, 1917.

Von Dungern and Hirschfeld[1] discovered that the groupings were inherited according to the Mendelian distribution. Ottenberg[2] has recently confirmed and extended this observation and suggested the use of blood tests as indicating the parentage of a child, for the child's group must fit with the group or groups of the parents.

The examination of a large number of people of different races has shown considerable variations in the percentage occurrence of the different groups. Whether this fact will permit the determination of racial origins is a question not yet settled. There is recent evidence, also, that there are subgroups in the original four, which can be detected by special methods. Group II, for example, may include three distinct types.[3]

In the selection of a donor for blood transfusion, the recipient's group must first be determined, after which a donor of the same group is selected and cross-tested. The determination is most easily accomplished by employment of stock sera of Groups II and III. The suspension of red cells of the recipient should be prepared by shaking three or four drops of blood in one cc. of citrated saline; a drop of serum of Group II is placed on a slide and mixed with a drop of the cell emulsion. The agglutination is looked for either with a magnifying glass or with a low microscopic magnification. Similar tests are carried out with Group III serum. If there is no agglutination, the recipient belongs to Group I; if both sera agglutinate, he belongs to Group IV; agglutination by Group II serum, but not by Group III, puts the recipient in Group III; agglutination by Group III serum, but not by Group II, shows the corpuscles belong to Group II. When a donor of the same group is obtained, a "cross test" should be carried out between the serum and the corpuscles of both donor and recipient, for it has been found that while in general individuals of the same group can be transfused, occasionally some slight incompatibility exists which, while not often serious, may still nullify some of the benefits of the transfusion. When standard sera are not available much time may be lost in selecting a donor, for then the serum of the patient has to be tested against the blood corpuscles of the potential donors and the latter rejected if any agglutination takes place. As the cells of Group I are not agglutinated by any sera, individuals of this group may serve as "universal donors," in spite of the fact that the cells of the recipient's blood may be agglutinated by the donor's serum; the chief danger of blood transfusion being in the agglutination of the donor's cells by the recipient's cells; but except in an emergency, transfusion should always be done between persons of the same group.

It is not safe to do a second transfusion between the same persons, even between two persons of like groups, because the first transfusion may result in the production of some slight amount of antibody, owing to a lack of perfect adaptation. Hence a subsequent uncontrolled transfusion may result in serious injury to the recipient. A Wassermann test must be made on all donors, as a number of syphilitic infections are known to have resulted from lack of observation of this rule.

FOREIGN BODIES IN THE BLOOD.

Various bodies which do not belong there, aside from those above mentioned, may find access to the vessels and mingle with the blood. Pus cells may get into the blood from the opening of an abscess into a vessel or from some inflammatory change in its walls. Desquamated endothelial cells from the vessel walls, either in a condition of fatty degeneration or in various stages of proliferation, may be mingled with the normal blood elements; also tumor cells of various kinds, fragments of disintegrated thrombi, portions of heart valves, etc. Megakaryocytes from the bone-marrow have been found after fractures, and syncytial

[1] *Von Dungern & Hirschfeld:* Ztschr. f. Immunitätsforsch. Orig., 1910, vi, 284.

[2] *Ottenberg:* J. Immunol., 1921, vi, 363; J. A. M. A., xxxviii, 873. See however for a criticism of the two factor theory, *Snyder, L. H.*, Jour. Am. Med. Assn., 1927, lxxxviii, 562.

[3] *Guthrie, Pessel & Huck:* Johns Hopkins Hosp. Bull., 1924, xxxv, 221 (bibl.).

cells after eclampsia. Crystals of bilirubin have been found in the blood in icterus, and Charcot-Leyden crystals have been seen post-mortem in the blood and bone-marrow of cases of leukemia.

Fat, in a moderate amount, is a normal ingredient of the blood, during digestion, and in lactation it is increased. Under pathological conditions it may occur in larger and smaller droplets. This *lipemia* occurs in diabetes, in alcoholism, in acute phosphorous poisoning, and in some cases of dyspnea from various causes. The droplets are small and liable to escape observation, but if the blood is kept a white layer of fat collects on the surface of the serum as it separates.

In many cases of injury, particularly in crushing fractures[1] of the bone, the fat of the marrow finds its way into the blood, and it may collect in large drops in the vessels of the lungs, forming the so-called *fat emboli* (Fig. 11, p. 41); or it may pass the lungs and form emboli in other parts, as the brain, kidneys, etc. Fat embolism in eclampsia is of occasional occurrence.

The fat may be absorbed from the vessels, having produced little or no disturbance; or in some cases it may produce serious results by the stoppage of a large series of vessels in the lungs, brain, or other parts of the body.[2]

Tissues and organs whose blood-vessels are suspected to contain fat droplets should be fixed in Müller-formol or 4 per cent. formaldehyde and thoroughly washed in water. Frozen sections are then treated with a mixture of equal volumes of Müller's fluid and 2 per cent. osmic acid, or stained with Sudan III (page 57). The sections should then be stained with hematoxylin and mounted in glycerin.

Air, as a result of an opening in the veins, is of occasional occurrence. If the amount of air be small, it appears to be readily absorbed, and does little or no harm. If, on the other hand, a large quantity is admitted to the veins at once, it collects on the right side of the heart, from which the contractions of the organ are unable to force it in any considerable quantity, and, the supply of blood being thus cut off from the lungs, death very quickly ensues. The blocking of the smaller pulmonary vessels and of the vessels of the heart with air bubbles may also hasten death. It is especially from wounds of the veins of the neck and thorax that the accident is most apt to occur. But it may be due to the introduction of air into the uterine veins during intrauterine injections or the removal of tumors.[3] Considerable quantities of air may be set free in the blood in caisson disease (page 22) due to the solution of nitrogen in the plasma under the increased pressure.

Parasites and other Foreign Bodies in the Blood.—The occurrence of animal and vegetable parasites is considered more in detail in parts of this book devoted to these organisms. It will suffice to mention here that the more important of the parasites found in the blood are: The Plasmodium malariæ, Trypanosomata, Filaria sanguinis hominis, the

[1] *Bissell, W. W.*, Jour. Am. Med. Assn., 1916, lxvii, 1926, has found as much as 3.75 gm. of fat per 100 c.c. of blood, the norm being not over 0.6 gm.

[2] For résumé of this subject, with bibliography, consult *Welch*, Embolism, Allbutt, System of Medicine, 1909, vi, 258. See, also, page 42.

[3] *Welch*, Allbutt, System of Medicine, 1909, vi, 254.

embryo of Trinchinella spiralis, the Spirillum obermeieri, and the Treponema pallidum.

The various forms of bacteria which may be found in the blood will be considered in parts of this book in which these organisms are treated in detail.[1] Parenchyma-cell emboli are considered on page 40.

Melanemia.—In this condition, which is most frequently the result of intermittent and remittent fever, particularly the severer forms, the blood contains larger and smaller, irregularly shaped particles or masses of brown or black pigment. The pigment may be free, but more often is inclosed in leucocytes, and may be deposited in the liver, spleen, lymph-nodes, bone-marrow, and blood-vessels, in consequence of which these organs may assume a gray or slate color. The condition may be transient in character, and may be accompanied by anemia and leucocytosis. The pigment developed in malaria originates in the decomposition of the hemoglobin under the influence of the plasmodium. Pigment which has been taken into the lungs from the air, such as coal dust, etc., may find its way into the blood either before or after deposition in the bronchial or other lymph-nodes, and may be afterward deposited in the spleen and liver.[2]

General Diseases Involving the Blood and Blood-Forming Organs.[3]

There is a group of diseases in which the most striking lesion seems to be an alteration in the composition of the blood, although in some members of the group other lesions are also present. This group embraces chlorosis, secondary and pernicious anemia, leukemia, and certain closely related, but still obscure conditions.

CHLOROSIS.

Chlorosis is a disease of the blood seen in women only and attended with a diminution in the hemoglobin, and usually in the number of the red blood-cells. Of late years the disease has become very rare.

Of the essential element in the incitement of this disease and of the exact method of its origin we are ignorant. The condition has been attributed to congenital hypoplasia of the heart and blood-vessels, to prolonged malnutrition, to intestinal intoxication, and to functional disturbance of an unknown nature in the blood-producing organs.

In the mildest grade of chlorosis the only change to be observed is a slight diminution of hemoglobin. In severer forms there may be added

[1] For methods and results of bacterial studies of the blood with bibliography, consult *Kühnau*, Ztschr. f. Hyg., 1897, xxv, 492; *Rosenberger*, Am. Jour. Med. Sc., 1903, cxxvi, 234; *Canon*, Die Bakteriologie des Blutes, Jena, 1905; *Lenhartz*, Die Septischen Erkrankungen, Wien, 1903. For method of demonstrating animal parasites see *Stäubli*, München. med. Wchnschr., 1908, lv, 2601; and *Warren* and *Herrick*, Am. Jour. Med. Sc., 1916, cli, 556.

[2] For further details concerning changes in the blood, consult *Simon*, Clinical Diagnosis, 9th ed.; Philadelphia, 1918; *Cabot*, Clinical Examination of the Blood, 5th ed., New York, 1904; or *Wood*, Chemical and Microscopical Diagnosis, 3d ed., New York, 1917.

[3] For a full discussion of the subjects treated in this chapter the reader is referred to *von Noorden*, Bleichsucht, Nothnagel's Spec. Path. u. Therap.; *Ehrlich* and *Lazarus*, Die Anaemie, ibid.; *Helly*, Die Hämatopoetischen Organe, ibid., and *Naegeli*, Blutkrankheiten und Blutdiagnostik, Leipzig, 1919.

a diminution in number and moderate variations in size and shape of the red cells. In very severe and relapsing cases the hemoglobin may be very much decreased, the color index falling even as low as 0.4; the red cells may number less than two millions per cubic millimeter, and the average size of the cells be less than normal. The leucocytes are not increased in number. There may be a slight relative increase of the lymphocytes; megalocytes, microcytes, and poikilocytes may appear (see Plate IV, Fig. 2). Polychromatophilia is frequent.

The specific gravity of the blood is diminished in proportion to the fall in hemoglobin; the total quantity is greatly increased. The time of coagulation is often very short, a change undoubtedly correlated with the not infrequent thrombosis seen in chlorosis. Even in cases of considerable severity the changes in the viscera characterizing other forms of anemia have been found wanting, although degenerative changes in the red cells may occur in accordance with the severity of the disease. The liver does not contain an excess of iron; the bone-marrow, in the few cases which have come to autopsy, has shown little or no hyperplasia; and the urine is free from pathological urinary pigments.

The regeneration of the blood in chlorosis under rest and treatment with iron may usually be rather promptly effected by increased activity of the red marrow, which is probably hyperplastic. This regenerative process may be indicated in the blood by the periodical appearance of considerable numbers of normoblasts. The appearance of these nucleated red cells may be accompanied by a moderate increase of leucocytes, both mononuclear and polynuclear. Myelocytes also may rarely be seen.

SECONDARY ANEMIA.

While chlorosis may be considered usually a disease of adolescence, and while its occurrence is confined to the female sex, there is another type of blood change which seems best classified under the heading of secondary anemia, and which is independent of sex or age. The determining agents are either of a general nature, such as poor food and bad air, or they are actual diseases, or they may be intestinal parasites, or, finally, chronic poisoning. Among those diseases which are likely to induce a well-defined anemia we may mention prolonged suppuration, mycotic endocarditis, diseases of the stomach and intestines, malaria, syphilis, and malignant tumors. The intestinal parasites are chiefly the Anchylostoma duodenale and the Bothriocephalus latus. The poisons are lead and, more rarely, arsenic. The alterations which are apparent on examining the blood are very variable, depending upon the agent. The hemoglobin is regularly diminished to a greater extent than the red cells; it may fall as low as 15 to 20 per cent.; the red cells rarely fall below one million. Nucleated red cells of the normoblastic type are frequent in the severe cases; megaloblasts are not found except in advanced cases of Bothriocephalus anemia. As a rule the average diameter of the red cells is slightly below normal, with a moderate

poikilocytosis. Granular degeneration is present to a variable extent in the red cells except in malaria and lead poisoning, when it is the rule. The threads and granules demonstrable by vital stains are present in many of the red cells after regeneration begins,[1] and their frequency above the norm of 2 to 3 per cent. may be taken as an index of the rate of repair. Such new-formed red cells, in contrast to mature forms, also

FIG. 303.—BONE-MARROW FROM SHAFT OF FEMUR FROM CASE OF SECONDARY ANEMIA DUE TO RECURRENT CARCINOMA.

The normal fat tissue is to a certain extent replaced by an edematous reticular connective tissue containing islands of nucleated red cells and myelocytes. The hyperplasia is not so extensive as that seen in leukemia or pernicious anemia, in which often all of the fat is replaced by the new growth of cells.

contain mitochondria.[2] In the anemias produced by the Bothriocephalus the blood picture may be that of pernicious anemia, with a great increase in the size of the cells and the appearance in the blood of numerous megaloblasts, thus forming an exception to the general rule that the blood of secondary anemia is normoblastic in type. In the anemia due to the Anchylostoma or the Uncinaria the blood shows the picture of a chlorotic anemia often accompanied by a considerable eosinophilia, which is not usually seen in the Bothriocephalus variety. The leucocytes are increased in anemia due to suppuration and in about 50 per cent. of the tumor cases; in other forms there is usually but little change in the number, though it is impossible to formulate a general rule (Plate IV, Fig. 3). When, however, a tumor invades the bone-marrow an extensive hyperplasia of this tissue may occur with consequent flooding of the blood current with large numbers of immature leucocytes so that the blood simulates that of myelogenous leukemia (Fig. 303).

[1] *Vogel, K. M.*, and *McCurdy, U. F.*, Arch. Int. Med., 1913, xii, 707 (bibl.).
[2] *Sappington, C. O.*, Arch. Int. Med., 1918, xxi, 695.

PERNICIOUS ANEMIA.

Pernicious anemia is a disease of the blood and blood-forming organs, characterized by excessive destruction associated with defective production of red cells.

The exact relation of the factors concerned in the causation of the disease has not been determined. It may be said, however, that while very rapid cases of pernicious anemia have been observed unaccompanied by the usual lesions in the bone-marrow associated with defective hematogenesis, the disease seems not to exist without excessive hematolysis. Despite the anemia the general metabolism of the body is increased.[1]

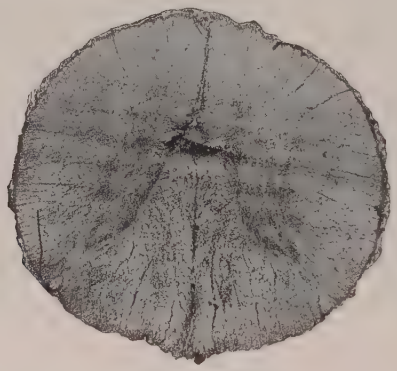


FIG. 304.—SUB-ACUTE COMBINED DEGENERATION OF CORD IN PERNICIOUS ANEMIA AFFECTING CHIEFLY POSTERIOR AND LATERAL COLUMNS.

The essential lesion is an extreme and progressive diminution in number and very great variation in size and form of the red blood-cells (as shown in Plate IV, Fig. 4). Nearly constant is a widely distributed lesion of the bone-marrow, in which the normal fatty marrow of the long bones is replaced by one containing an excessive number of large nucleated red corpuscles or megaloblasts. The destruction of hemoglobin is followed by a considerable deposit of iron in the liver, spleen, marrow, and other organs, and by the appearance of excessive amounts of urobilin in the urine. The prolonged anemia may be accompanied by fatty degeneration in the viscera, especially of the liver, kidneys, and heart muscle. As a combined result of fatty changes in the arterial walls and of the diminution in albuminous ingredients and in the coagulability of the blood, hemorrhages in various parts of the body, especially the retina, are of frequent occurrence. Disseminated areas of sclerosis (Fig. 304) in the spinal cord are not infrequent and are regarded as the result of minute hemorrhages in this region.[2] The spleen is usually small, but may be normal in size, and in some instances is slightly enlarged. Microscopically there is but little change of note. The Malpighian bodies are normal; there is no increase in interstitial tissue. As a rule, a large

[1] *Meyer* and *DuBois*, Jour. Am. Med. Assn., 1916, lxvii, 440.
[2] *Reese* and *Beigler*, Am. Jour. Med. Sci., 1926, clxxi, 194.

number of nucleated red cells may be found, and some phagocytosis of red corpuscular débris in large phagocytic cells; but, on the other hand, this phagocytosis may be entirely absent morphologically, and the spleen may differ but little from the norm.

The bone-marrow contains nucleated red cells of all types mingled with many non-granular myelocytes. Granular myelocytes are apt to be more abundant in the centers of the ribs and bodies of the vertebræ, where normal hematogenesis still persists. Areas of new formation of red cells and myelocytes[1] are not infrequent in the spleen and liver, but are rare in the prevertebral lymph-nodes.

In the blood the red cells are usually reduced to less than two millions and occasionally to half a million per cubic millimeter. Of the remaining cells a considerable percentage may be abnormally large (megalocytes), or very small (microcytes). Cells of very irregular shape are often present in abundance (poikilocytes) (Plate IV, Fig. 4). The quantity of hemoglobin in the majority of the cells is usually increased, but may be diminished in a certain proportion of cells, which then resemble those found in chlorosis. The hemoglobin or color index—that is, the relation of the total percentage of hemoglobin to the total number of cells—may be normal when a deficiency of hemoglobin in one cell is counterbalanced by a proportionate excess in another, but in general it is greater than unity.

A variety of degenerative changes in the red cells is commonly present, including especially those alterations in the staining reactions of the protoplasm known as *polychromatophilia* and *granular degeneration*. In the first the cell stains a more or less uniform blue with methylene blue; in the second the cells contain granules which give a strong basophilic staining reaction.

Nucleated red cells of normal size (normoblasts) are of frequent occurrence in the blood of well-established pernicious anemia. Abnormally large nucleated red cells (megaloblasts) are a nearly constant element at some stage of the disease and are of great diagnostic importance, as they indicate the presence of a grave lesion in the bone-marrow. They are more abundant than the normoblasts in well-developed cases.

Megalocytes and megaloblasts usually show an excess of hemoglobin, may exhibit ameboid movement, and have no tendency toward the formation of rouleaux. Extremely large nucleated red cells (gigantoblasts) are frequently found in advanced cases, and in these cells as well as in the megaloblasts the nuclei may be rarely seen in various stages of normal or pathological mitosis. Blood crises, by which term is indicated the appearance of large numbers of normo- or megaloblasts in the circulation, may occur in pernicious anemia, but it must be remembered that the blood picture in any severe anemia varies much from day to day without any marked alteration in the general condition of the patient. In the absence of complications producing leucocytosis in pernicious anemia, the leucocytes are usually diminished in number. There is a

[1] *Meyer* and *Heineke*, Verhandl. d. deutsch. path. Gesellsch., 1906, ix, 224.

relative increase in the number of lymphocytes, and usually a few myelocytes may be found.

Spontaneous remissions in the course of the disease are frequently seen. Permanent recovery is, however, only an evidence of an incorrect diagnosis. Excision of the spleen has been practised on the theory of a splenic origin of the hemolytic toxin, but without avail as to the ultimate result, though temporary amelioration unquestionably occurs.[1] Transfusion, also, has been of temporary benefit when performed fairly often.[2] Extraordinary benefit follows a special diet.[3]

Aplastic Anemia.—A very rare variety of a rapidly fatal form of anemia has been described in which the number of red cells is diminished without the blood showing the changes characteristic of pernicious anemia. The bone-marrow in these cases has been found to be fatty instead of hyperplastic as is the typical marrow of pernicious anemia. It has been suggested that the bone-marrow for some unknown reason had not responded to the call made upon it by the rapid hematolysis taking place in the disease, and therefore did not undergo the megaloblastic changes so characteristic of the bone-marrow in well-marked cases of pernicious anemia.[4] A very similar picture is produced by the exhibition of benzol, which is a leucotoxin especially but also diminishes the production of the red cells and blood-platelets.[5] Prothrombin is reduced and a purpuric condition may ensue if the drug is pushed.[6]

LEUKEMIA (LEUKOCYTHEMIA).

Leukemia is a disease in which the characteristic changes are an alteration in the relative proportions of the different leucocytes of the blood, with usually an increase in their number, and the appearance of certain forms not seen in the circulation under normal conditions. The red cells are diminished in number, and abnormal forms appear in the blood. Accompanying these alterations in the circulating blood are changes in the bone-marrow, less often in the spleen and in the lymph-nodes. Its inciting factors are still unknown. Leukemia may be classed in four types, which are fairly well defined clinically and morphologically, but between these there exist many transitional forms, especially from the point of view of the morphology of the blood. These four types are the acute and chronic lymphatic leukemia and the acute and chronic myelogenous leukemia (*splenomyelogenous*).

Acute Lymphatic Leukemia is a disease resembling clinically an acute infection, with a rapidly increasing anemia, enlargement of the lymph-nodes, as a rule, and a moderate increase in the size of the spleen and liver. Cases are on record, however, in which there was no enlarge-

[1] For a study of the influence of splenectomy on metabolism in anemia, see *Denis, W.*, Arch. Int. Med., 1917, xx, 79.

[2] *Percy, N. M.*, Surg., Gynec., and Obst., 1917, xxiv, 533; *Minot* and *Lee*, Boston Med. and Surg. Jour., 1917, clxxvii, 761; and *Yates* and *Thalhimer*, Jour. Am. Med. Assn., 1926, lxxxvii, 2156.

[3] *Minot* and *Murphy*, Jour. Am. Med. Assn., 1926, lxxxvii, 470.

[4] For a study of a series of such cases, see *Lavenson, R. S.*, Am. Jour. Med. Sc., 1907, cxxxiii, 100.

[5] *Selling, L.*, Zieglers Beitr., 1911, li., 576.

[6] *Hurwitz* and *Drinker*, Jour. Exper. Med., 1915, xxi, 401.

ment of the spleen or lymph-nodes.[1] The blood changes are very characteristic. The red cells diminish rapidly in number, normoblasts and occasionally megaloblasts are present, and the leucocytes are increased, though usually below 100,000. The forms present are chiefly lymphocytes, either large or small, the large, as a rule, predominating. While the staining reactions of the large lymphocytes in this disease correspond with those of the cells of normal blood, yet it has been shown[2] that in another group of large non-granular-cell leukemias, cells of a

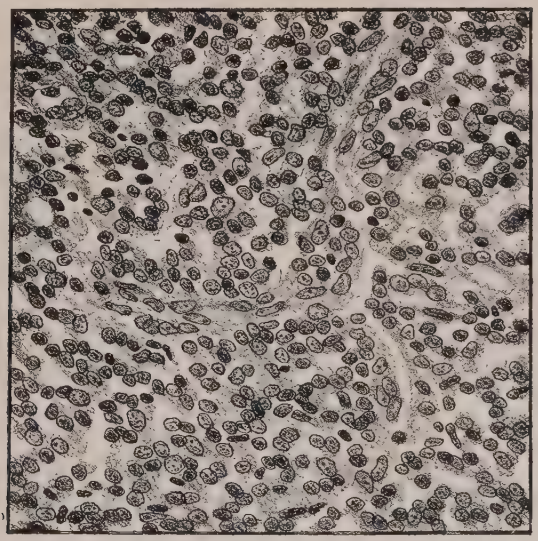


Fig. 305.—Skin Nodule from Case of Acute Lymphatic Leukemia.

lymphocytic aspect contain a proteolytic and lipolytic ferment characteristic of the granular types of cells from the bone-marrow. This has been confirmed[3] by the discovery that in the large lymphocytes it is possible to demonstrate an oxidase, a ferment heretofore considered to be confined to the granular types. These findings indicate that the cells in question should be considered rather as myeloblasts than as large lymphocytes. The bone-marrow is altered to a tissue showing large numbers of lymphocytes, the so-called lymphoid hyperplasia, which often extends to the lymphoid tissue in the viscera and may lead to the formation of nodules in the skin (Fig. 305). In several cases of acute lymphatic leukemia, a bacillus corresponding to that found in Hodgkin's disease has been present in the lymph-nodes. It is probably without etiological significance.[4]

[1] *Kelly*, Univ. Pennsylvania Med. Bull., 1903, xvi, 270.
[2] *Longcope* and *Donhauser*, Jour. Exper. Med., 1908, x, 618.
[3] *Schultze, W. H.*, München. med. Wchnschr., 1909, lvi, 167; and *Peters, J.*, ibid., p. 1478.
[4] *Simon* and *Judd*, Jour. Am. Med. Assn., 1915, lxiv, 1630 (bibl.).

Chronic Lymphatic Leukemia.—The blood shows a severe anemia with great increase in the lymphocytes. The small forms of the lymphocytes are most abundant, in contradistinction to the acute type of the disease, in which the large forms are usually in excess. The lymph-nodes and spleen are usually enlarged; the bone-marrow is in a condition of lymphoid hyperplasia, and there are lymphoid infiltrations in the various organs (see Fig. 306 and 307 and Plate IV, Fig. 5).

Acute Myelogeneous Leukemia.—A few cases of leukemia of the myelogenous type have been reported in which the clinical course was very acute, with a rapidly increasing anemia and the occasional appear-

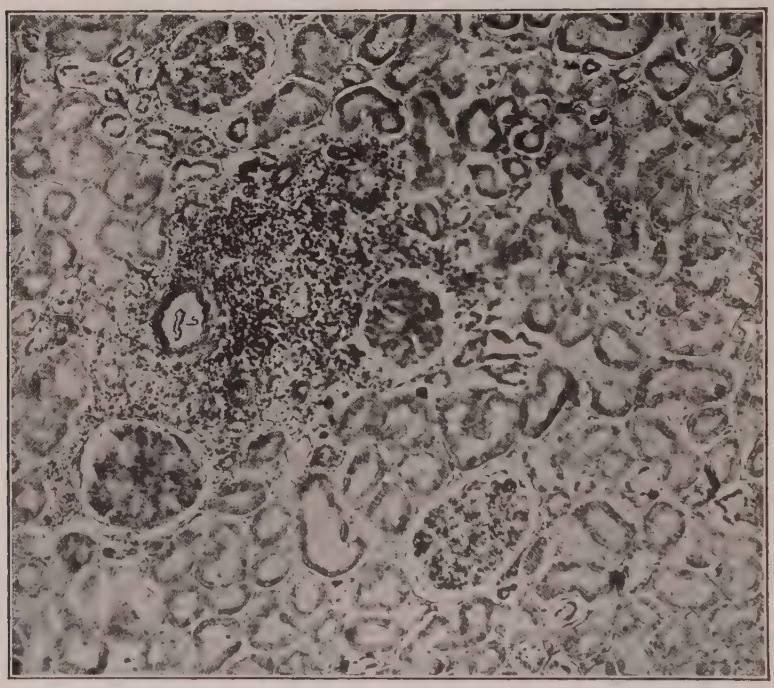


Fig. 306.—Leukemic Infiltration of Kidney in Case of Lymphatic Leukemia.

ance of nucleated red cells. In some of the cases the blood was not characteristic and the diagnosis could be made only after death by a study of the changes in the bone-marrow; in others the blood picture resembled that of a chronic myelogenous leukemia with the usual large percentage of myelocytes. Some of the cases diagnosed as acute myelogenous leukemia were undoubtedly of the type of disease known as chloroma, while others were presumably acute infections with a high leucocytosis and the appearance of a few myelocytes in the blood with a marked hyperplasia of the bone-marrow due to the prolonged septic condition.[1] The difficulties in the diagnosis of acute myelogenous leu-

[1] *Herz*, Akute Leukämie, Vienna, 1911 (bibl.); *Sternberg, C.*, Wien. klin. Wchnschr., 1911, xxiv, 1623.

kemia are complicated by the fact that the lymphocytes in acute lymphatic leukemia may be greatly diminished toward the end of the disease, and a few myelocytes may appear under these conditions, thus rendering a differentiation impossible.[1]

Chronic Myelogenous Leukemia.—The blood shows a severe anemia, rarely of a pernicious type, with marked quantitative and qualitative changes in the leucocytes. The increase in number of white cells may be to more than one million per cubic millimeter. Myelocytes, both neutrophilic and eosinophilic, are quite constantly present in considerable numbers. They may form a large proportion of the leucocytes

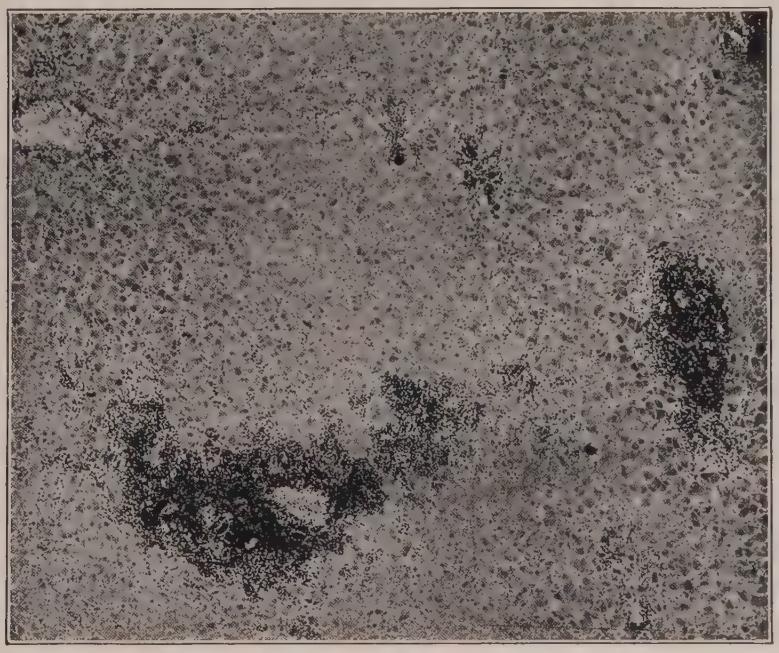


FIG. 307.—LIVER FROM A CASE OF LYMPHATIC LEUKEMIA.
Showing infiltration of the organ with leucocytes. The large collections are in Glisson's capsule, but small numbers are seen between the liver cells.

present. Basophile cells are very abundant in cases of long duration, especially the type with polymorphic nuclei, myelocytes with basophilic granulations being rare. In rapidly advancing cases mitoses may rarely be seen in the red cells and in the leucocytes (see Plate IV, Fig. 5).

The pathological forms of leucocytes in myelogenous and lymphatic leukemias have little or no ameboid motion. This explains the interesting fact that the pus from an abscess in a leukemic subject contains only the polynuclear neutrophile cells found in such exudates in persons with a normal blood condition. In acute infections and after treatment with radium or the Roentgen rays, the number of myelocytes present in

[1] *Billings* and *Capps*, Am. Jour. Med. Sc., 1903, cxxvi, 375.

the circulation may be greatly reduced and the blood may even lose the cell forms characteristic of leukemia, the myelocytes being replaced by lymphocytes or the ordinary polynuclear leucocytes of normal type.

The same condition may be seen in mild cases, which may under treatment reach a point in which it is difficult to make a diagnosis from the blood alone.

In this connection it must be remembered that the blood picture in pernicious anemia and the leukemias is a very variable one. As a rule, more than one examination is necessary for a certain diagnosis, and it must not be forgotten that occasionally a case, apparently of pernicious anemia, may go on to a typical lymphatic or myelogenous leukemia.

In myelogenous leukemia there is hyperplasia of the bone-marrow, which usually fills the shafts of the long bones with a firm, pink mass composed largely of myelocytes. This hyperplasia may involve the whole bone-marrow of all the long bones, or it may be confined to irregular, scattered areas, so that one should be critical in accepting reports of cases of leukemia without bone-marrow changes. The other organs may rarely show hyperplasia of lymphoid tissue, often especially well marked in the gastrointestinal tract, while scattered through the spleen are often seen numerous small areas containing myelocytes. In advanced cases the spleen is almost wholly transformed into myeloid tissue. Infarcts and perisplenitis are frequent. The liver is usually enlarged.

There is some reason to think that in the spleen, for instance, extensive multiplication of the cells goes on in the so-called "marrow cell or myeloid metastases." While it is generally assumed that these deposits correspond very closely to tumor deposits, one school of pathologists holds that mesenchymal tissue anywhere in the body may return to its fetal function and give rise to myelocytes. Attention is called also to the fact that myeloid changes in the sites just mentioned may occur when there is but little hyperplasia of the marrow, and it is pointed out that in myelogenous leukemia it may be possible temporarily to reduce the blood to a normal condition by the application of radium or Roentgen rays to the spleen alone. In the blood, spleen, and marrow, after death, elongated octahedral crystals (called Charcot-Leyden crystals) are occasionally found. Hemorrhages into the serous and mucous membranes and the retina, especially the latter, are more or less frequent; and fatty degeneration of the viscera is a constant expression of the impoverished condition of the blood. For more detail concerning the lesions of the organs see chapters on spleen, lymph-nodes, bones, etc.

CHLOROMA.

Under this name, which means merely "a green tumor," are grouped a number of forms of a disease which shows many points of resemblance to both malignant tumors and the leukemias.[1] It is now generally con-

[1] *Dock, G.*, Am. Jour. Med. Sc., 1893, cvi, 152; *Dock* and *Warthin*, Med. News, 1904, lxxxv, 971, and *Sternberg, C.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix, 360. *Lehndorff* (Ergebn. d. inn. Med., 1910, vi, 221) gives a very complete discussion of all the published cases to date, amounting to about ninety, and a copious bibl.; see also *Burgess*, Jour. Med. Research, 1912, N. S. xxii, 133 (bibl.)

sidered to belong to the group of primary diseases of the hematogenetic organs, its closest relationship being with the leukemias. The important lesions are the presence of new growths of a greenish color in the osseous system, accompanied in many cases by alterations in the circulating blood. The tumors are frequently observed in the bones of the skull, but may involve any of the organs of the body. Nothing is known as to the chemical relationships of the coloring matter.

Two chief types of tumors can be distinguished histologically, the lymphoid and the myeloid. In the lymphoid form the tumor and its metastases are composed of cells resembling lymphocytes, generally of the large variety. Diffuse infiltration of the other organs may also occur, resembling that seen in the leukemias. In the myeloid type the tumor is characterized by the presence of large cells resembling the myelocytes or myeloblasts of the bone-marrow. In this form widespread involvement of the bone-marrow and spleen is apt to occur, and extension to other organs generally takes place in the form of small nodules of myeloid tissue (see, also, page 1094).

The blood pictures may be conveniently divided into four types: One with small lymphocytes; one with large lymphocytes, which is the most frequent type; one with atypical large mononuclear cells resembling myeloblasts; and one in which the myelocytes are the cells most abundantly present. The red corpuscles also show the changes due to an anemia.

Unless definite superficial tumors are present it is often impossible to differentiate the blood picture from that of a leukemia, and many of the cases have been diagnosticated only after death by the finding of greenish tumors scattered throughout the organs.

PSEUDOLEUKEMIA. (Hodgkin's Disease, Adénie.)

For a consideration of pseudoleukemia and Hodgkin's disease see pages 560 and 561.

ANEMIA INFANTUM PSEUDOLEUKEMICA. (Von Jaksch.)

This is a somewhat peculiar from of anemia occurring in children, and characterized by a progressive course, by a considerable increase of leucocytes, by enlargement of the spleen and liver, and often by hyperplasia of the lymph-nodes. A large number of nucleated red cells are present in well-marked cases. Myelocytes are found, but rarely form more than 10 per cent. of the white cells.

By some authorities it is regarded as an early stage of leukemia or as a type of leukanemia, by others as a form of secondary anemia following rachitis, tuberculosis, or syphilis, the marked blood changes being considered as due merely to the greater lability of the infant's hematopoietic system.

The histological changes in the blood-forming organs are, so far as is known, very similar to, but less pronounced than, those of leukemia.[1]

[1] *Evans, F. A.*, and *Happ, W. M.*, A study of so-called infantile splenic anemia or anemia infantum pseudoleukemica. Bull. Johns Hopkins Hosp., 1922, xxxiii, 1 (bibl.).

SPLENIC ANEMIA.

A very chronic form of anemia with enlargement of the spleen was first described by Banti.[1] The course of the disease may be divided into three stages; one in which there is marked anemia with increase in the size of the spleen and irregular attacks of fever, the white cells remaining normal in number and proportion. This period is usually from three to five years, but may be much longer. Then follows an interval of a few months in which there are jaundice and gastrointestinal disturbances, passing into the final stage with fever, jaundice, ascites, diminished leucocytes, extreme anemia, and often severe hemorrhages from the gastrointestinal tract. The chief lesions are a very much enlarged spleen with induration of the splenic pulp, atrophy of the Malpighian bodies, and frequently, though not always, an extreme sclerosis of the portal and splenic vessels. The sinuses are often dilated and may contain large cells filled with phagocyted red corpuscles. A moderate interlobular cirrhosis of the liver is usually present, but is not of a high grade. In the earlier stages no cirrhosis can be made out. Changes have not been observed in either the lymph-nodes or the bone-marrow.

Originally the condition was considered merely an abnormal cirrhosis of the liver with enlargement of the spleen, but study of many cases in recent years, together with the striking improvement noticed after splenectomy, has forced the conclusion that the splenic lesion is the most important and that the cirrhosis is largely a secondary phenomenon.

Umber[2] has described an extremely interesting case in which there was apparently an extensive toxic destruction of the protein material in the body. After excision of the spleen this destruction was checked and the protein balance became positive.

Despite the improvement resulting from splenectomy and the lack of correspondence in the clinical course of the disease, there has been much opposition directed of late against the consideration of Banti's disease as a distinct pathological entity. Some observers hold, apparently without sufficient evidence, that syphilis is entirely responsible for the splenomegaly;[3] others, having demonstrated the Bacillus hodgkini in the spleen, claim a bacterial origin for the condition;[4] while a third group believes that the splenomegaly is due to a "fibrogenetic toxin probably of intestinal origin."[5] It is evident that more investigation is needed to clear up this complex subject.

In the type of splenomegaly described by Gaucher, there may be severe anemia, usually of a chlorotic type. Nucleated red cells are rarely seen; normoblasts have been reported in only two instances, and megaloblasts in but one. The leucocytes are usually diminished in number, but may

[1] *Banti*, Zieglers Beitr., 1898, xxiv, 21; *Lossen*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1904, xiii, 753. For a very careful study of the remarkable improvement in the blood following splenectomy, see *Bierring* and *Egdahl*, Jour. Am. Med. Assn., 1906, xlvii, 1149 (bibl.).

[2] *Umber*, Ztschr. f. klin. Med., 1904, lv, 289.

[3] *Norris, Symmers*, and *Shapiro*, Jour. Am. Med. Assn., 1918, lxx, 191.

[4] *Yates, Bunting*, and *Kristjanson*, Jour. Am. Med. Assn., 1914, lxiii, 2225.

[5] *Moschcowitz, E.*, Jour. Am. Med. Assn., 1917, lxix, 1045 (bibl.).

be normal in amount or even increased. Percentual differences are not very marked. (For a description of the lesions of the spleen, see page 581.)

Other types of splenomegaly accompanied by anemia are occasionally seen in adults, and in some instances the focus of the disease seems to be limited to the spleen, but there is no reason to consider the condition as worthy of a separate classification. Many of the cases ultimately prove to be obscure forms of lymphatic leukemia in which the characteristic blood pictures appear only a few days or weeks before death. Other forms are due to a splenic tuberculosis or syphilis. In children, rickets, syphilis, and chronic gastrointestinal lesions are the chief causes of splenic enlargement with anemia.

A separate class of splenic anemias heretofore included in this group has been shown to be due to a parasite, the Leishmania donovani (page 143). The splenic anemia frequently occurring in children in Southern Italy and Northern Africa has been shown by Nicolle to be due to a similar parasite, the Leishmania infantum (pages 143 and 586).

A marked relative lymphocytosis characterizes the blood of both of these conditions. The parasites can be found in the blood in about a half of the adult cases, but in children they are very scanty. In blood obtained by splenic puncture the parasites can, however, be easily found in both forms.

Sickle Cell Anemia.—A peculiar disease often, but not always, accompanied by anemia, and so far only recognizable in the Negro race, is that in which the red cells assume a sickle shape. Apparently the disease occurs in widely varying degrees of severity. In some of the patients the anemia is minimal and the condition is little more than an anomaly of the red cells without symptoms, and in others the anemia is severe. In dry smears only a few of the red cells may show this peculiar malformation, but in sealed preparations of blood after twenty-four hours a large proportion of the red cells may assume sickle shape. There is some evidence that the cause of the change lies not in the cells themselves but in a constituent of the plasma. In the anemic type, reticulated and nucleated blood cells are usually present in the blood and an increased number of blood plates. The resistance of the red cells to hemolytic agents may be normal or increased. Phagocytosis of red cells by monocytes has been observed in smears from the peripheral blood. The anemia is of the hemolytic type, with jaundice, increased urobilin in the urine, and bilirubin in the blood. The spleen is not usually enlarged, though in one case it was hypertrophied and showed multiple infarcts. The most frequent lesion of the spleen is the atrophy of the pulp either diffuse or in plaques with sclerosis of the connective tissue. Many of the splenic cells contain granules giving an iron reaction. There may be hyperplasia over limited areas of the splenic pulp giving rise to discrete reddish islands visible to the naked eye. The bone marrow is moderately hyperplastic. Renal lesions are a very frequent accompaniment of the disease. The sinusoids of the liver may contain myelocytes and nucleated red cells. The Kupffer cells contain phagocyted red cells and pigment giving the

iron reaction. Some type of subacute or chronic infection may accompany the condition, which evidently has a toxic etiology acting on a racial peculiarity. There is some evidence that the disease has an hereditary basis.[1]

[1] *Graham, G. C.*, Arch. Int. Med., 1924, xxxiv, 778 (bibl.); *Cooley* and *Lee*, Am. Jour. Dis. Child., 1926, xxxii, 334.

CHAPTER II.

THE LYMPH-NODES.

General Characteristics of the Lymph-Nodes

It is well, in studying the lesions of the lymph-nodes, to remember that they are structures so placed in the course of the lymph-vessels that the lymph, in flowing toward the larger central trunks, passes through them, undergoing a sort of filtration as it percolates through the trabeculæ of the lymph-sinuses. If this fact be borne in mind the lesions of the lymph-nodes, which are in the majority of cases secondary, are much more readily understood. Particles of pigment, cells from malignant tumors, fragments of dead or disintegrating cells either free or within phagocytes, red blood-cells, bacteria, etc., which in any way get into the lymph-vessels, are carried along until a lymph-node is reached, and here they are, in part at least, deposited among the trabeculæ of the sinuses, or are taken up by phagocytic endothelial cells, while the lymph passes on and out of the efferent vessels. Soluble toxic substances also are carried into the lymph-nodes, often inciting marked and significant alterations.[1]

The lymph-nodes as blood-forming organs stand in close relationship to many abnormal processes in the body. In them are produced a large proportion of the lymphocytes of the circulating blood.

What is called *lymphatic tissue* embraces not only the so-called lymph-glands and the less complex but still well-defined structures found in the stomach, intestines, tonsils, and elsewhere, and called lymph-follicles, but also the less well-defined, irregular masses of tissue resembling that of lymph-follicles, which, as Arnold[2] has shown, are widely disseminated in variable amounts in different parts of the body: in the lungs, beneath the pleura, in the thyroid, salivary glands, liver, kidneys, etc. Although the exact nature of these more diffuse masses of lymphatic tissue is too little understood, as indeed is that of the lymph-follicles and glands themselves, there is reason to believe that they are analogous structures and prone to be affected by similar deleterious agencies. It seems better, in view of the fact that the so-called lymph-glands are not glands at all, in the ordinary sense of the word, to call them *lymph-nodes*, and the smaller masses of lymphatic tissue scattered through various parts of the body *lymph-nodules* instead of "lymph-follicles."[3]

There is considerable variation in the situation, number, and size of lymph-nodes in special regions of the body, and they vary in size with age. It may be said that the lymph-nodes are most fully developed in the adult, and undergo fatty degeneration and involution in old age.[4] In infancy myeloid tissue is present.

Finally the lymph-nodes are built up of cells many of which have not achieved a high degree of differentiation and thus are prone to undergo mitosis and rapid proliferation, when, from infective or destructive processes in regions to which they minister, deleterious agents gather in their recesses.

HEMOLYMPH-NODES.

Numerous observers have described the occurrence in man and certain of the lower animals, under normal as well as pathological conditions, of structures which

[1] For a study of bacteria in normal lymph-nodes, see *Kälble*, München. med. Wchnschr., 1899, xlvi, 622; in abnormal nodes, see *Torrey*, Jour. Med. Research, 1916, N. S. xxix, 1.

[2] *Arnold, J.*, Virchows Arch., 1880, lxxx, 315; 1880, lxxxii, 377; 1881, lxxxiii, 289; 1882, lxxxvii, 114.

[3] For a study of the structure of lymph-nodes, see *Weidenreich*, Arch. f. mikrosk. Anat., 1905, lxv, 1.

[4] For a study of regeneration of lymph-nodes and vessels, see *Meyer*, Bull. Johns Hopkins Hosp., 1906, xvii, 185 (bibl.); *Bayer*, Arch. f. klin. Chir. (Langenbeck), 1895, xxxix, 637, and *Hammerschlag, R.*, Virchows Arch., 1908, cxciv, 320 (bibl.).

resemble lymph-nodes, but are usually smaller and are red or mottled red and white. In man they are found especially in the prevertebral fat, in the deep cervical region, in the retroperitoneal region, near the renal vessels, and about the brim of the pelvis. They are normally present, but they may be more conspicuous under certain pathological conditions—pernicious anemia, acute infections, intoxications, etc. Their color is due to the presence of blood in the sinuses of the nodes. There are numerous transitional forms between nodes containing lymph-sinuses only and those which more nearly resemble the spleen in character. They become more prominent and are increased in number after splenectomy in animals.[1] These structures do not appear to be lymph-nodes in which blood has accumulated from hyperemia or hemorrhage, and by some are considered to be structures entirely independent of the lymphatic system.[2]

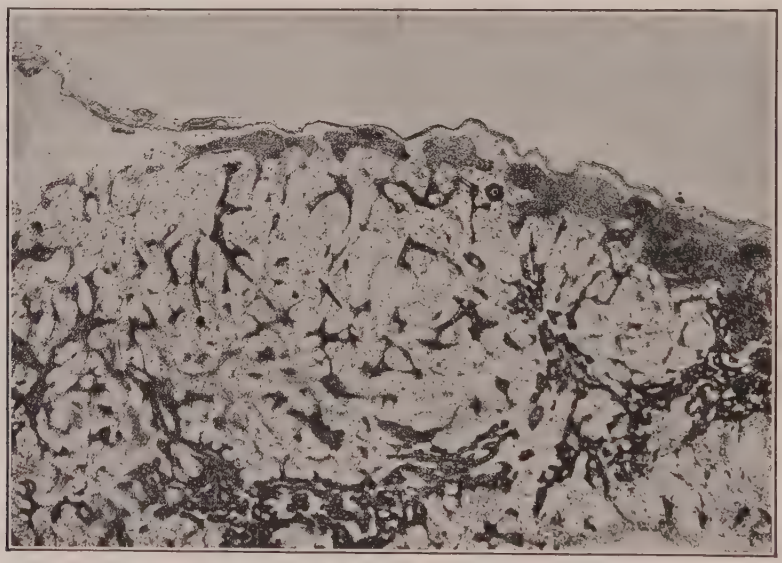


Fig. 308.—Edema of a Lymph-node—Typhoid Fever.
The perifollicular lymph-sinuses are widely distended with clear fluid. The lymph-nodules and lymph-cords are flattened from pressure of the fluid.

ATROPHY.

Atrophy is a very regular occurrence in old age. In this condition the nodes are small, hard, and, unless pigmented, light in color. Microscopical examination shows a marked diminution in the number of parenchyma cells, while the reticulum and the capsule and trabeculæ and the elastic fibers may be thickened. In the nodes of the peritoneal cavity, fatty replacement of the lymphoid structure is frequent in a variety of diseases; while in senile atrophy the fat accumulates about the shrunken node.

[1] See *Warthin, A. S.*, Jour. Med. Research, 1901, N. S. i, 3; 1902, N. S. ii, 435 (bibl.); and Vaughan Anniversary Contribution to Medical Research, 1903, p. 216. For a full and excellent summary, with bibliography, consult *Warthin, A. S.*, Trans. Chicago Path. Soc., 1902, v, 151. For a study of the development of hemolymph-nodes in adipose tissue, see *Dayton, H.*, Am. Jour. Med. Sc., 1904, cxxvii, 448.

[2] *Weidenreich*, Anat. Anz., 1902, Ergänzungsheft, xxi, 47; *Meyer*, Jour. Exper. Zool., 1914, xvi, 241.

EDEMA.

Edema of the lymph-nodes may be associated with a blocking of the associated lymph-vessels. Under these conditions the lymph-sinuses may be widely distended (Fig. 308).

DEGENERATION.

Amyloid degeneration of the blood-vessels and reticulum of the lymph-nodes occurs under the conditions which favor this change in general. It may occur in connection with amyloid degeneration of other parts of the body, or by itself. It may occur in nodes otherwise normal, or in those which are the seat of other lesions—thus in simple chronic or tuberculous inflammation. It is frequently found in the mesenteric

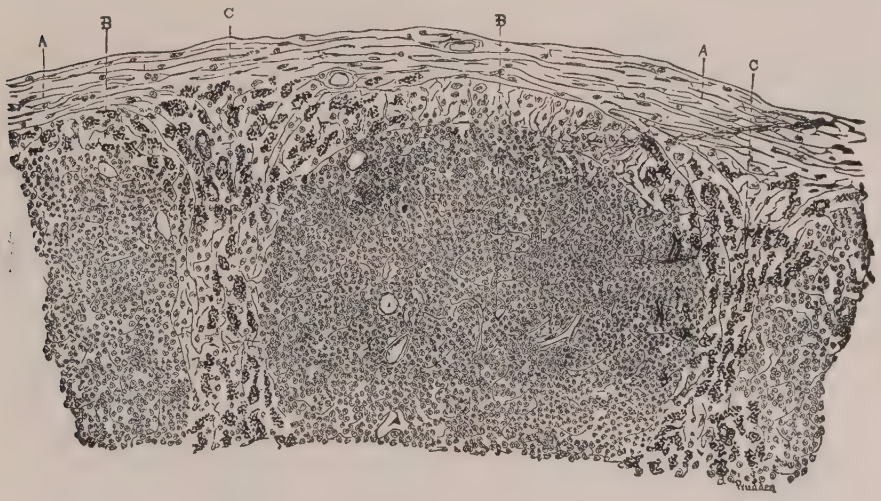


FIG. 309.—PIGMENTATION OF BRONCHIAL LYMPH-NODE.
The pigment is largely in the lymph-sinuses and inclosed in cells. *A*, Capsule of node; *B*, lymph-nodule; *C*, perifollicular lymph-sinuses.

lymph-nodes, in connection with waxy degeneration of the intestinal mucous membrane. Syphilis frequently causes this disease.

Hyaline degeneration of the external layers of the smaller arteries and the capillaries and reticulum of the lymph-nodes occurs occasionally in old age or in connection with wasting diseases, especially tuberculosis.

PIGMENTATION.

The pigment which is very frequently found in lymph-nodes may be derived from the hemoglobin of the blood, either in the nodes themselves or in remote parts, or it may be formed of various materials introduced into the body from without, such as the pigments used in tattooing, respired dust particles of various kinds—coal, stone, iron, etc. (Fig. 309). The pigment particles, which usually lodge first in the lymph-sinuses,

may collect here in large quantities, either in the reticulum or in the cells lying in its meshes; they may penetrate the follicles and cords and find permanent lodgment there. They usually induce a greater or less degree of chronic inflammation, so that in extreme cases, such as are frequently seen in the bronchial lymph-nodes, nothing is finally left of the node, but a more or less deeply pigmented mass of dense connective tissue. The function of the node may be, of course, in this way partially or entirely destroyed. The pigment in these cases appears to reach the node, in part by being carried along free in the lymph current, in part through transportation by leucocytes in which the particles have become inclosed. Pigmentation of the nodes is most marked in those about the root of the lungs, which are frequently of a mottled gray or a black color, but it

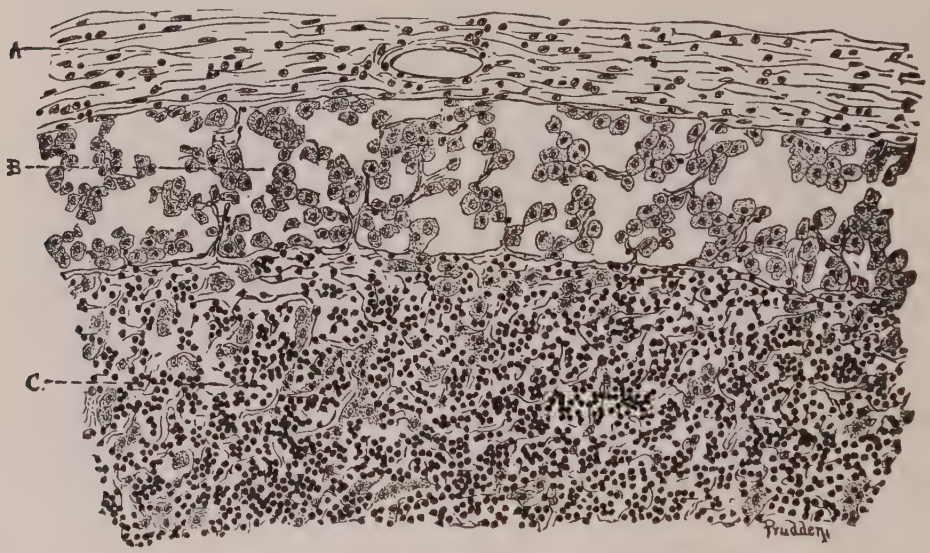


FIG. 310.—ENDOTHELIAL HYPERPLASIA OF LYMPH-NODE IN TYPHOID FEVER.

Showing a portion of one of the mesenteric nodes. *A*, Capsule; *B*, perifollicular space or lymph-sinus, containing in its meshes many large cells; *C*, portion of one of the nodules, with large and small cells in the meshes of its reticulum.

may occur in the mesenteric and other nodes. Under similar conditions the diffuse lymphatic structure in the lungs and liver may be pigmented.

INFLAMMATION.

Acute inflammation of the lymph-nodes is commonly due to the presence of pathogenic microorganisms or of toxic substances, usually bacterial in origin, which may be formed in the node or brought to it in the lymph current from the tributary region of the body. Under these conditions the nodes are usually swollen, reddened, and softer than normal, and are often the seat of small hemorrhages. One or all of the nodes of a cluster may be affected.

Two forms of the acute inflammatory process may conveniently be recognized, a HYPERPLASTIC and an EXUDATIVE.

In the HYPERPLASTIC form a microscopical examination shows the lesion to be largely due, in addition to the hyperemia and hemorrhage, to a proliferation of the cells of the node, the spheroidal mononuclear cells of the nodules and cords, and especially the endothelial cells of the lymph-spaces (Fig. 310), which may increase in number and exfoliate to such an extent as to fill and largely distend the lymph-sinuses. These endothelial cells often contain red blood-cells, leucocytes, and fragments of other cells (Fig. 311). In diphtheria, scarlatina, and typhoid fever, as well as in many other infectious diseases, necrosis of the hyperplastic tissue is common. The necrosis is usually in circumscribed areas—focal necrosis—and often involves especially the germinal centers of the nodules.

After simple hyperplasia of the lymph-nodes, resolution readily occurs. But if necrosis have taken place, such areas may be replaced by fibrous tissue.

This form of lesion of the lymph-nodes is common. It may occur in the cervical nodes with many forms of angina; in the inguinal nodes in connection with acute infectious processes in the external genital organs; in the axilla with infectious processes in the hand, arm, or breast; in the mesenteric nodes with infection or intoxication of intestinal or other origin. Similar lesions occur in the solitary lymph-nodules and Peyer's patches of the intestine (Fig. 312).

In EXUDATIVE or *suppurative* forms of inflammation of the lymph-nodes, in addition to the simple hyperplastic changes just described, there are emigration and collection of leucocytes, with the formation of more or less fibrin in the lymph-sinuses as well as in the interstices of the nodules. The capsule of the nodes may be infiltrated with exudate. With these changes there may be necrosis and softening of the tissue of the nodes and the development of abscesses. Small abscesses may coalesce, and thus a considerable part of the node be converted into a suppurating necrotic mass—*bubo*. Such a bubo may open externally or into the surrounding tissue and heal by granulation tissue and cicatricial tissue; its contents may be absorbed or become dry and dense and calcified, and surrounded by fibrous tissue. Suppurative inflammation of the lymph-nodes often occurs in connection with suppurative processes elsewhere, in pyemia, venereal infection, etc.

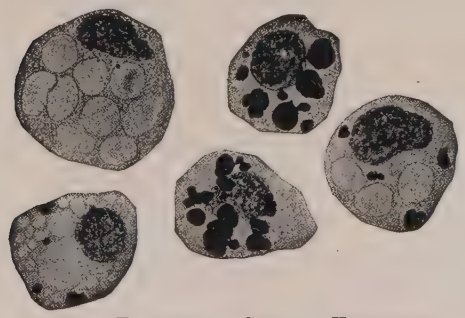


FIG. 311.—ENDOTHELIAL CELLS IN HYPERPLASIA OF THE LYMPH-NODES.

The exfoliated cells contain red blood-cells, fat droplets, and masses of blood pigment.

The lymph-nodes of children are, as a rule, more readily involved in infectious processes of other parts than are those of adults.

Chronic Inflammation.—This is characterized by the increase of the connective-tissue elements of the node, with a gradual and commensurate disappearance of the lymphoid cells. The reticulum of the folli-

cles and sinuses becomes thickened and fibrous, and in the trabeculæ and capsule new connective tissue is formed, until, in advanced cases, the entire node may be more or less extensively converted into a mass of fibrous tissue. This condition is very frequently seen in the lower tracheal

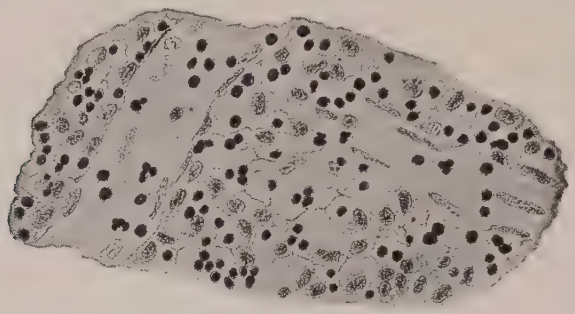


Fig. 312.—Hyperplasia of Peyer's Patch in Typhoid Fever.
Showing new-formed endothelial cells in the meshes of the reticular tissue between the blood-vessels.

and in the bronchial nodes, apparently as a result of the lodgment in them of respired pigment particles; but it may occur in any nodes, either as a result of repeated moderate degrees of inflammation or from causes which we do not know. In some cases the nodes are greatly enlarged

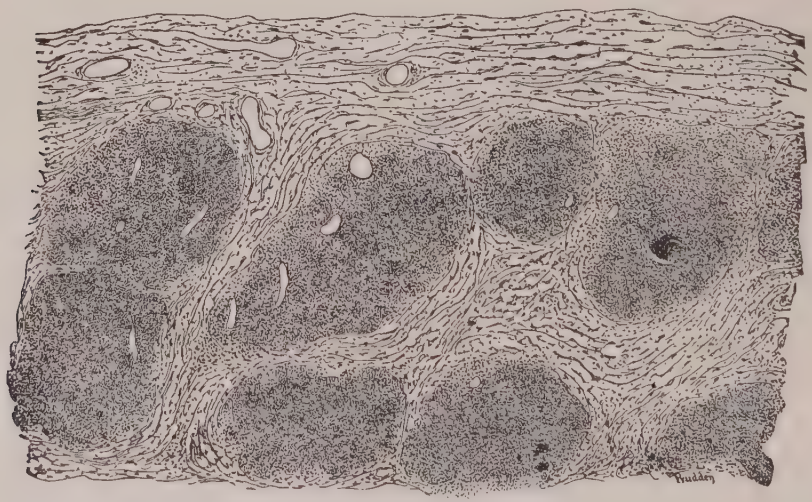


Fig. 313.—Chronic Inflammation of Bronchial Lymph-node.
Showing obliteration of the lymph-sinuses and atrophy of the lymph-nodules by the new-formed connective tissue.

and the new tissue contains many large cells, while in other cases the connective tissue is dense and contains but few cells (Fig. 313).[1]

Tuberculous inflammation may be local, confined to the nodes, or it

[1] Consult *Ribbert*, Ueber Regeneration und Entzündung der Lymphdrüsen, Zieglers Beitr., 1889, vi, 187.

may occur in connection with general acute miliary tuberculosis, or with tuberculous inflammation of single organs. It may occur in single nodes, or in several nodes of the same group, or in groups situated in different parts of the body. In its simple and acute form there may be no evident change to the naked eye in the appearance of the nodes, or they may be besprinkled with small, grayish white, translucent spots. Under these conditions the nodes may be reddened and soft, or swollen and denser than normal. In more advanced forms of the lesion the tubercles coalesce and undergo a greater or less degree of cheesy degeneration. Under these conditions the cheesy areas are evident to the naked eye as more or less sharply circumscribed, opaque, whitish or yellowish areas, frequently surrounded by an irregular, more translucent, grayish zone of tubercle tissue which merges insensibly into the adjacent tissue. The entire node may become involved, and more or less completely converted into a cheesy mass, in the periphery of which a zone of tubercle tissue may or may not be evident.

Microscopically the small nodules or miliary tubercles are seen to consist of more or less circumscribed collections of small spheroidal, or more frequently larger polyhedral cells, with or without well-defined giant cells. They usually commence to form in the follicles and lymph-cords of the nodes, and from these may spread and involve the entire surrounding tissue. The cheesy degeneration, which here as elsewhere is apt first to involve the central portions of the tubercles, presents the usual appearances. Tubercle bacilli may be found in the edges of the cheesy areas or in the tubercle tissue about them.

Simple inflammatory changes regularly occur in the periphery of the tubercles. There is an increase of cells in the lymph-sinuses and follicles, and a more or less marked swelling, and apparently a proliferation of the cells of the reticular tissue of the node. In cases in which the process is chronic there is often marked increase of the connective tissue of the nodes, the reticular tissue becomes dense and fibrous, and the trabeculæ and capsule are thickened. The tubercles themselves, instead of undergoing cheesy degeneration, may become fibrous or be converted into a hyaline material.

The cheesy material may dry and shrink, and become inclosed by a capsule of dense connective tissue and become calcified; or it may soften, and thus cavities be formed in the nodes, filled with grumous material; or inflammatory changes may be induced in the vicinity of the nodes, leading to abscesses. On the other hand, hyperplastic inflammation in the periphery of the affected nodes may result in their becoming bound together into a dense nodular mass.

The formation of bone in lymph-nodes has been described in connection with tuberculous inflammation, carcinoma, and other lesions.[1]

Scrofula.—Tuberculous inflammation of the lymph-nodes, especially in those of the cervical,[2] bronchial (Plates V and XI), and mesenteric groups, often occurs in children, particularly in those who are ill-

[1] See *Merkel, H.*, München. med. Wchnschr., 1905, lii, 1238.

[2] For bibliography of cervical tuberculous lymph-nodes, see *Dowd*, Ann. Surg., 1899, xxix, 559.

nourished. Northrup and Bovaird found in an analysis of 200 cases of tuberculosis in children that the lungs and bronchial lymph-nodes were involved in 148.[1] Such persons, in addition to the lesion of the lymph-nodes, are very liable to suffer from chronic tuberculous and other inflammations of the mucous membranes, skin, periosteum, joints, and the subcutaneous and other connective tissues. This general condition is known as *scrofula*, and the lesion of the nodes is sometimes called *scrofulous inflammation*.

While in many cases the portal of entry of the tubercle bacilli is not evident, and the lesions often present the appearance of hyperplasia of the lymphoid tissue with cheesy degeneration and the formation of more or less dense fibrous tissue rather than the typical characters of tuberculous tissue, nevertheless miliary and other forms of tuberculous inflammation are often present in so-called scrofula, and tubercle bacilli, while sometimes absent, are often present and virulent.[2]

The necrotic portions of such cheesy lymph-nodes in scrofula may soften and break down, and by the establishment of purulent and necrotic inflammation about them abscesses may form which may open externally. These abscesses may heal; but usually the healing is difficult and slow, and long-continued suppurations, frequently with the development of fistulæ, are very common. Instead of softening, the cheesy material in the nodes may become dry and hard and undergo calcification.

Generalized Tuberculous Lymphadenitis.—Several cases have been recorded of extensive tuberculous hyperplasia of the lymph-nodes in various parts of the body, the lesion resembling in its gross characters that of Hodgkin's disease. While in some of these cases the morphology of the lesions is characteristic of tuberculosis, in others the new tissue is diffuse and consists largely of new-formed, small, spheroidal and polyhedral cells with large multinuclear cells, and of fibrous tissue. The new-formed cells may undergo necrosis. Thus the tuberculous nature of the lesion is not always plain, even on microscopic examination. Animal inoculations are often necessary for the establishment of the nature of such cases.[3] The predilection of tubercle bacilli for lymph-nodes and the occurrence in them of the earliest lesions as a result of multiplication of the bacteria is apparently not in harmony with Bartel's theory that lymph-nodes are protective or with Murphy's belief that the lymph-cells act as inhibitory agents.[4]

Syphilitic Inflammation.—The lesions of the lymph-nodes which occur in connection with syphilis vary greatly, depending upon the stage of the disease. In the primary stage the nodes in the region of the seat of

[1] For a study of tuberculous bronchial lymph-nodes in children consult *Northrup*, New York Med. Jour., 1891, liii, 203; and *Bovaird*, ibid, 1899, lxx, 1. See further, *Marfan*, *Bouchard*, and *Brissaud*, Traité de Médecine, 1901, vii, 525. For later study of tuberculosis of lymph-nodes, especially in childhood, see *Harbitz*, Jour. Infect. Dis., 1903, ii, 143, ibid., 1917, xxi, 196.

[2] In the examination of lymph-nodes for tubercles and tubercle bacilli it should be remembered that not infrequently, though one fails to find either morphological tubercles or stained bacilli, the inoculation of portions of the fresh tissue into guinea-pigs will show that living and virulent bacilli were present.

[3] For a study of this form of tuberculosis, consult *Crowder*, New York Med. Jour., 1900, lxxii, 443, 490, (bibl.).

[4] *Smith, Theobald*, Jour. Am. Med. Assn., 1917, lxviii, 669, 764.

infection are apt to present the lesions of an ordinary acute inflammation occasionally with suppuration.

In the secondary stage of the disease the nodes of other regions, neck, elbow, axilla, etc., are often swollen and hard. Hyaline changes are common. There may be an increase of connective tissue in the capsule and trabeculæ, but the chief change is the accumulation in the follicles and lymph-sinuses of larger and smaller spheroidal and polyhedral cells. The reticular tissue may be thickened and the walls of the blood-vessels infiltrated with cells. In this condition the nodes may remain for a long time, not tending to form abscesses; or they may undergo resolution through degeneration and absorption of the cells.

In the tertiary stage of the disease the nodes may be the seat of chronic inflammation characterized by the formation of gummata. Under these conditions they may form large, firm nodular masses from the growing together by new connective tissue of several altered nodes. The gross and microscopical characters of gummata of the lymph-nodes are, in the main, similar to those in other parts of the body.

HYPERPLASIA OF THE LYMPH-NODES. (Lymphoma.)

In addition to the enlargement of the lymph-nodes due to types of inflammation which have been described above, there is still another variety, a tumor-like swelling of the nodes whose etiology is still in doubt, though the general assumption is that an infectious agent underlies the changes. The disease affects either a single node or a group; usually in the cervical region, the axilla, or the groin. The enlarged node or nodes remain discrete and, except for the discomfort consequent upon the tumor, have little or no influence on the health of the patient, and may persist for years. Such nodes on cut section are paler and firmer than the normal tissue. They are usually provided with a fairly thick capsule. Microscopically, they are composed of lymphoid tissue, preserving in general the anatomical divisions of the normal node. The germinal centers may be diminished in size, or greatly increased and show evidence of hyperplasia. There is no tendency of the lymphoid cells to invade the surrounding tissue. The lymphocytes themselves preserve morphological and functional qualities the same as the normal, though usually they are less compactly distributed between the connective tissue trabeculæ. The trabeculæ also are apt to be somewhat thicker than usual.

Small nodes with chronic hyperplastic inflammatory changes are frequent in the drainage areas of benign and malignant tumors of the glandular organs. This chronic hyperplasia is unquestionably due to the absorption of metabolic products from the gland secretion, or the tissue breakdown of the tumor. They disappear if the tumor is removed. Such nodes rarely reach a large size.

In the disease known as *status lymphaticus*, the lymph-nodes are often enlarged to a considerable size in association with a persistent and enlarged thymus. The microscopic changes in these nodes are chiefly those of a hyperplasia with increase in size of the germinal centers.

LEUKEMIC LYMPHOMATA.

In the different types of leukemia, chiefly in the lymphatic form, changes in the lymph-nodes are frequent. In acute lymphatic leukemia, especially in children, there is often considerable enlargement of the lymph-nodes usually in the neck, axilla, or groin, but often also of the internal nodes, tonsils, and other lymphatic areas in the body. Such nodes are often, though not always, discrete and movable, and do not involve the overlying skin. The capsule is as a rule infiltrated with cells, the substance of the gland is usually very soft and may be hemorrhagic, especially in acute leukemia. In more chronic cases, a considerable fibrous hyperplasia may occur so that the nodes are fairly firm. Microscopically, these nodes show either very great hyperplasia of the normal lymphocytes with more or less loss of the nodal architecture, or the replacement of the normal tissue by more or less extensive areas of large cells resembling the large lymphocytes found in the circulating blood.

In myelogenous leukemia distinct enlargement of the nodes is not very frequently met with, and when the process does occur the nodes will be found to have undergone a myeloid metaplasia with replacement of the lymphoid tissue with that resembling bone-marrow; in other words, with cells of a granular type. The change begins with the appearance of small areas of myelocytes. These gradually increase in size and displace the lymph-follicles, and finally the entire node may be replaced by the myeloid structures. Usually such nodes are soft and do not undergo fibrous changes. These nodular enlargements must be distinguished from the metastatic or tumor-like collections of lymphocytes which form in the skin in certain cases of acute lymphatic leukemia. Such nodules do not appear to occur in the myelogenous type, though they may be simulated by areas of subcutaneous hemorrhage, which when sectioned, owing to the large number of myelocytes in the exuded blood, resemble very closely the lymphatic tumors. An examination of the blood gives the clue to the nature of both the lymphatic and the myelogenous lymphomata. In specimens in which there is no record of the blood count, a careful examination should be made of the contents of the larger blood-vessels in the sections.

PSEUDOLEUKEMIC LYMPHOMATA.[1]

In another type of diffuse enlargement of the lymph-nodes coexisting leukemic changes in the blood do not occur, though a moderate anemia may exist. Individual nodes, or a large number, may be simultaneously involved, or the process may be progressive, spreading from one region to another. The nodes may fluctuate in size from time to time, as in leukemic enlargements. There is no tendency for the tumors to break down or soften, nor for the neighboring nodes to fuse. They are smoothly

[1] For bibliography of the subject with gastro-intestinal cases, see *Biggs* and *Elliott*, J. A. M. A., 1924, lxxxiii, 178.

encapsulated and usually fairly firm and pale on section. The bone-marrow is not as a rule altered, though in some cases the same leukemic overgrowth may be found as in the nodes.

Microscopically, the tumors resemble those of lymphatic leukemia, though they may contain a large number of eosinophile cells (Fig. 314). Whether a myeloid pseudoleukemic enlargement of the lymph-nodes may occur is still questionable.[1] In rare instances a leukemic blood condition

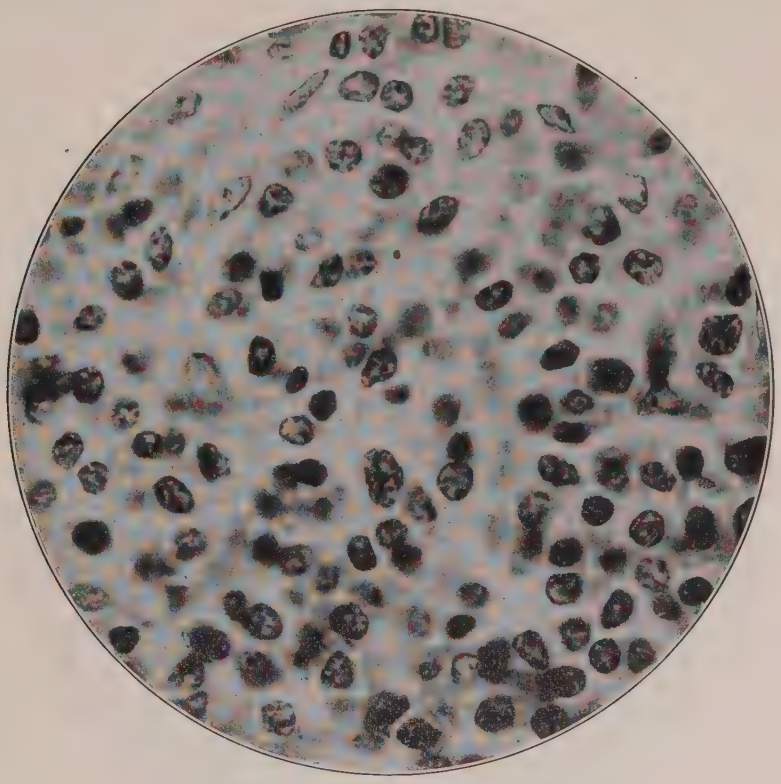


FIG. 314.—LYMPH-NODE FROM CASE OF CHRONIC LYMPHATIC LEUKEMIA. Compare with lymph-nodes in Hodgkin's disease.

develops after the pseudoleukemia has existed for a considerable time.[2] Metastatic myelomata should not be confused with a myeloid leukemic or psuedoleukemic lymphoma.

HODGKIN'S DISEASE. (Lympho-granulomatosis.)

In this relatively frequent disease, the changes in the lymph-nodes are entirely different from those previously described. Originally it was thought to be a diffuse tuberculosis of the lymphatic system, and unquestionably such a lesion may occur with the clinical picture of

[1] *Hirschfeld*, Berl. klin. Wchnschr., 1908, xlv, 2227.
[2] *v.Domarus*, Folia hæmatologica, 1908, vi, 337.

Hodgkin's disease, though the bacilli can usually be demonstrated only by animal inoculation.[1] The disease may be simulated also by diffuse metastases from an internal unrecognized tumor, but the microscopical examination of the nodes will differentiate the conditions.

The tumor-like swellings of Hodgkin's disease usually involve the superficial nodes of the neck, axilla, inguinal, or cubital regions, but the lesion may be confined entirely to the bronchial or retroperitoneal nodes. In some cases the spleen is very slightly affected; in others extensive necroses with a fibrous tissue replacement may occur, and instances have

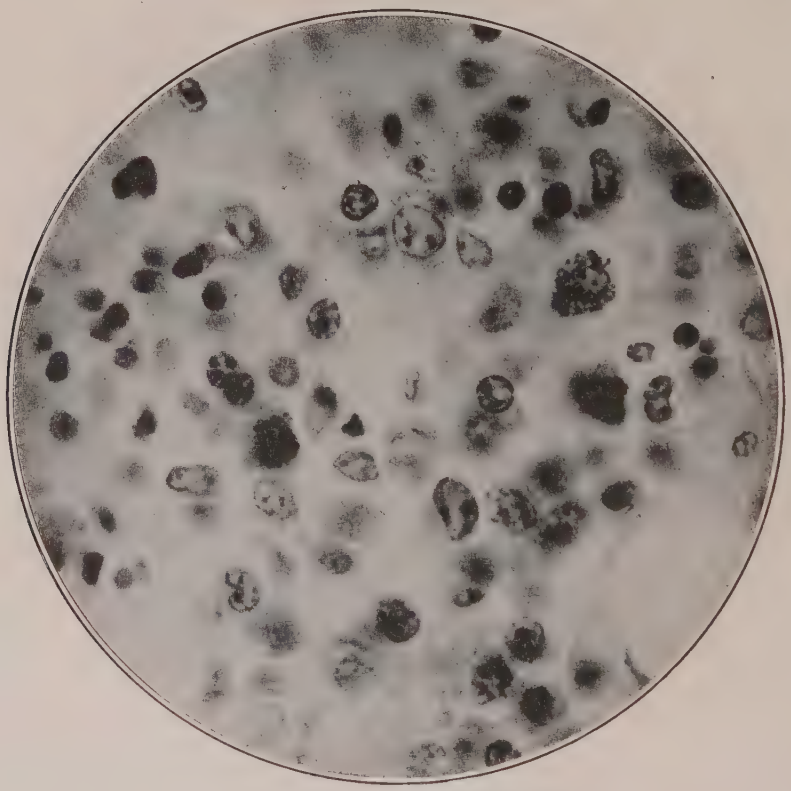


Fig. 315.—Bone-marrow in Hodgkin's Disease.
Showing eosinophile cells in great abundance.

been reported in which the splenic lesion seems to have been primary.[2] The bone-marrow shows a moderate hyperplasia or, occasionally, areas of giant cells and fibrosis with local eosinophilia (Fig. 315). In advanced cases the liver may show a few of the characteristic nodules (Fig. 316). The uterus[3] and, rarely, the skin (Fig. 317),[4] may show the characteristic

[1] *Sternberg* (Ztschr. f. Heilk., 1898, xix, 21) has made a careful study of cases of this type.
[2] *Mellon*, Am. Jour. Med. Sc., 1916, cli, 625.
[3] *Jessup, D. S. D.*, Proc. New York Path. Soc., 1912, xii, 3.
[4] *Arndt, G.*, Virchows Arch., 1912, ccix, 432 (bibl.); *Alaerson, H. E.*, Jour. Cutan. Dis., 1917, xxxv. 481.

lesion. The gross appearance of the nodes is considerably altered from the normal. They may be lobulated, soft or hard, and white, gray, or red, and often show areas of necrosis. They are usually entirely discrete, and there is no infiltration of the capsule or perinodular fat with lymphocytes as is the case in the forms of enlargement due to leukemia or lymphosarcoma. At first the only lesion, besides a moderate hyperplasia, may be the development of areas containing a considerable number of

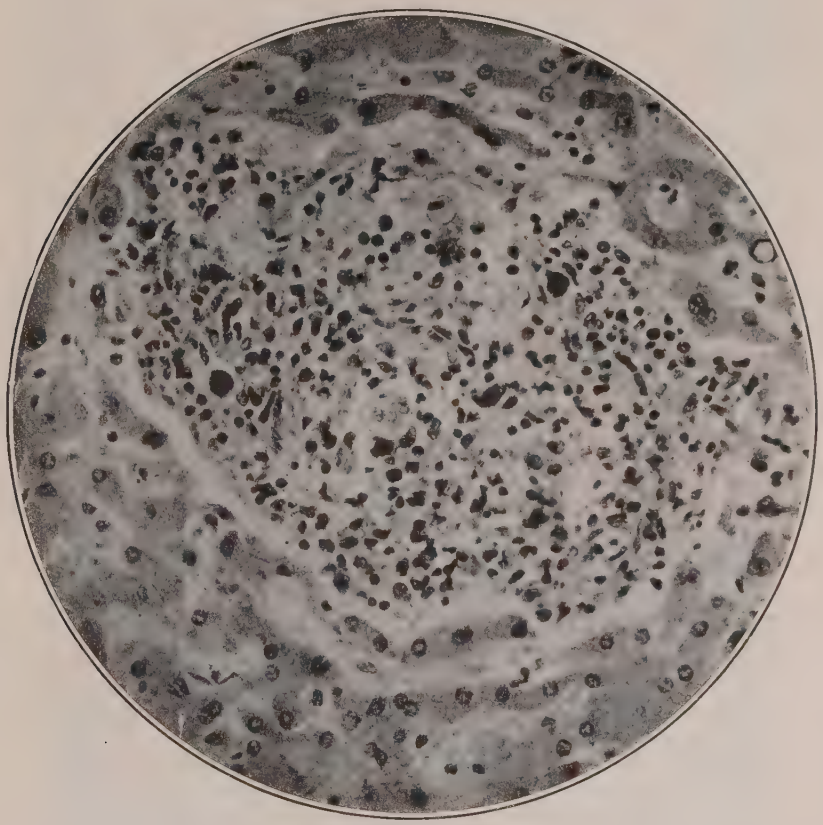


FIG. 316.—HODGKIN'S DISEASE. NODULE IN LIVER

The abdominal and bronchial lymph-nodes alone were involved in this case. The hyperplasia in the liver is of the same type as that in the nodes; with the formation of connective tissue and large irregular multinucleated cells.

large cells with a faintly staining cell body and a single large nucleus, sometimes showing mitosis (Fig. 318 and 319). In this early stage these cells correspond closely in morphology with the large cells of the germinal centers; they are not the same as the multinucleated cells of the later development of the disease. Not all the enlarged nodes show these changes equally well. Such alterations in the structure can scarcely be considered as specific, since they may be found in nodes undergoing

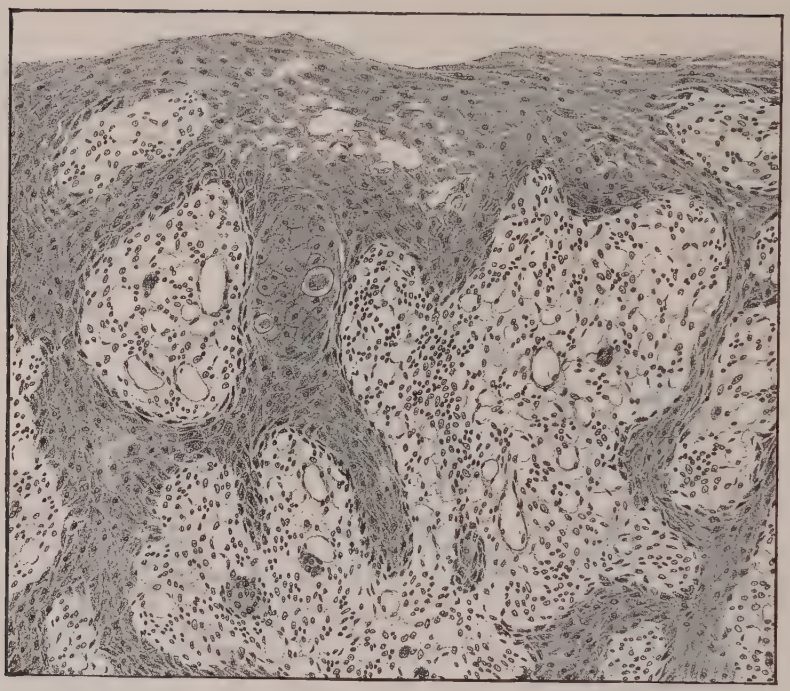


Fig. 317.—Hodgkin's Disease of Skin.

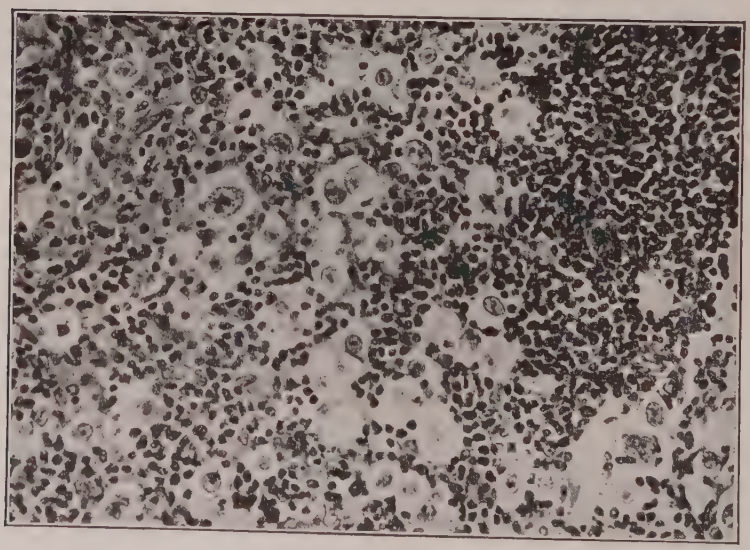


Fig. 318.—Hodgkin's Disease. Lymph-node with Lymphoid Tissue still Preponderating, but the Large Endothelial Cells Show Hyperplasia.
There is only a moderate connective tissue replacement.

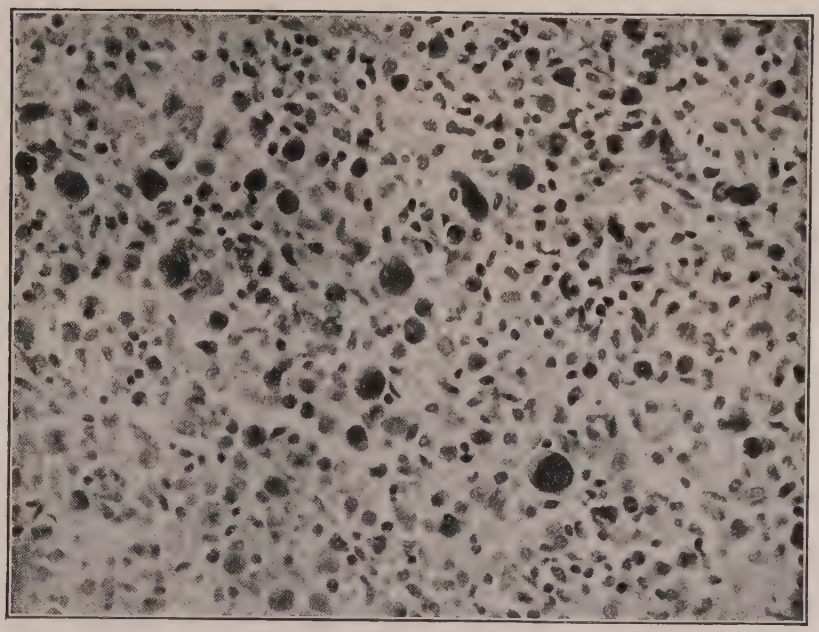


Fig. 319.—Hodgkin's Disease. Lymph-node Showing Extensive Hyperplasia of Large Cells

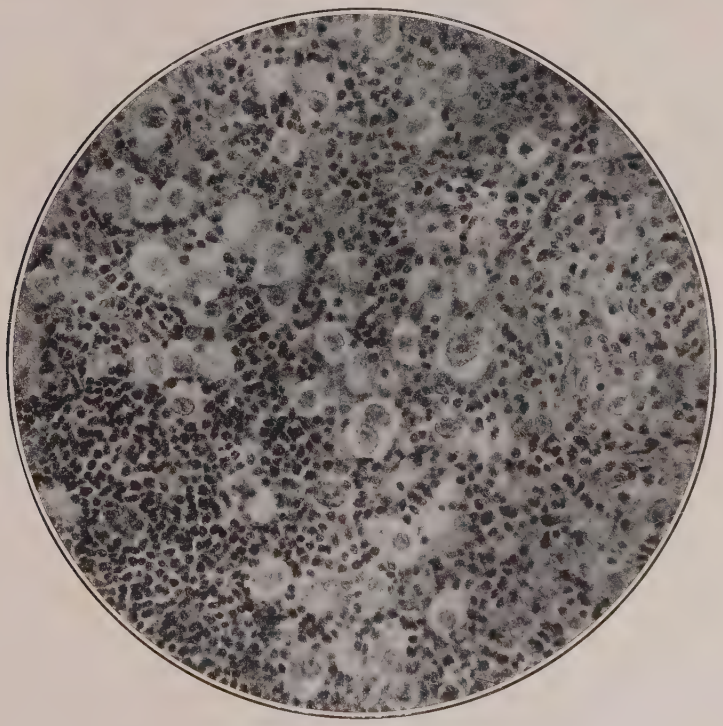


Fig. 320.—Hodgkin's Disease. Lymph-node in which the Lymphoid Tissue Still Predominates, but the Large Endothelial Cells show Hyperplasia.
There is a beginning connective tissue replacement.

chronic hyperplasia in response to the irritation of a neighboring malignant epithelial growth, or even after long continued chronic inflammation.

In the second stage, however, the diagnosis is usually possible from an individual node, for there are present not only the large cells before mentioned, but necrotic areas surrounded by cells of the epithelioid type (Fig. 320) and more or less numerous large cells with polymorphic nuclei or with two or more small oval nuclei lying in the center of the cell body. True giant cells of the Langhans' type (see Fig. 156, p. 291)

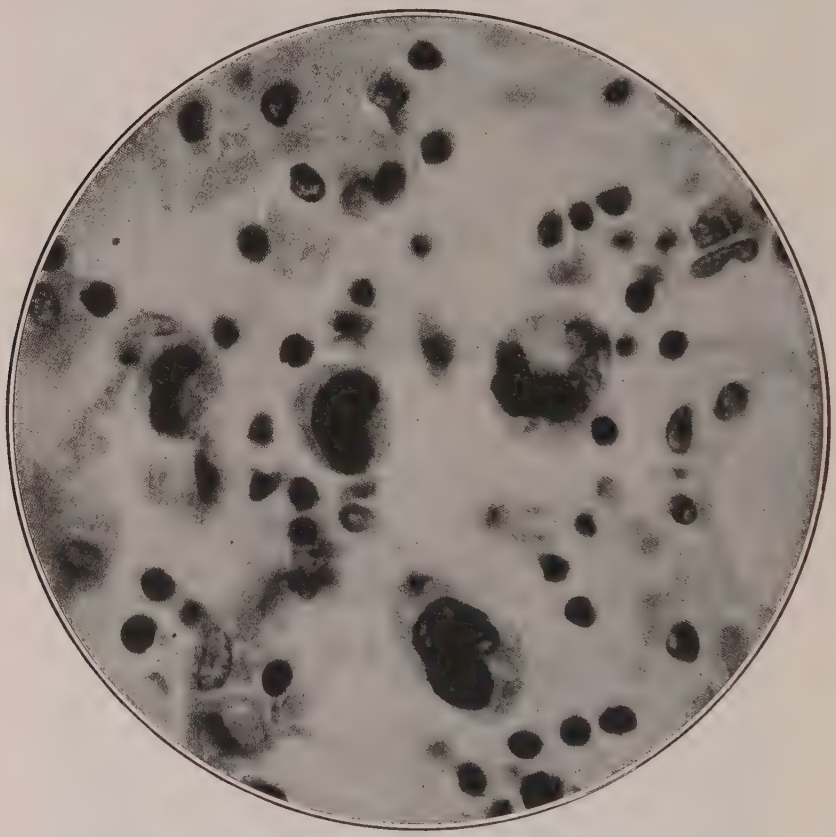


Fig. 321.—Hodgkin's Disease. Lymph-node showing Large Cells.

with peripherally arranged nuclei are rare in comparison with the other form (Fig. 321). This group of cells is probably produced by hyperplasia of the reticular endothelial cells. Necrosis in the nodes and spleen in these cases may be very extensive. There is usually a beginning replacement hyperplasia of the fibrous tissue of the reticulum.

In the third stage the nodes may be smaller than the previous stages, and are composed very largely of dense anastomosing bands of fibrous tissue which occasionally undergo hyaline degeneration (Fig. 322). Thrombosis or extensive obliterative endarteritis of the vessels is not

uncommon, and the lymphoid tissue may project under the endothelium so as nearly to close the lumen. The lymphoid tissue is occasionally reduced to a few scattered areas surrounded by dense connective tissue (Fig. 323).

Eosinophile cells may be abundant in the nodular substance, and sometimes an increase in eosinophiles is seen in the circulating blood; but neither condition is constant. Plasma cells also may be found in the nodes in large or small numbers. Lymphoid infiltration in the organs, such as is seen in leukemia, is not usually found. In fact, an important characteristic of Hodgkin's disease is that the lesions have a tendency to remain in nodular form and not to destroy the organ involved completely, if we except the lymph-nodes. There is always a severe pro-

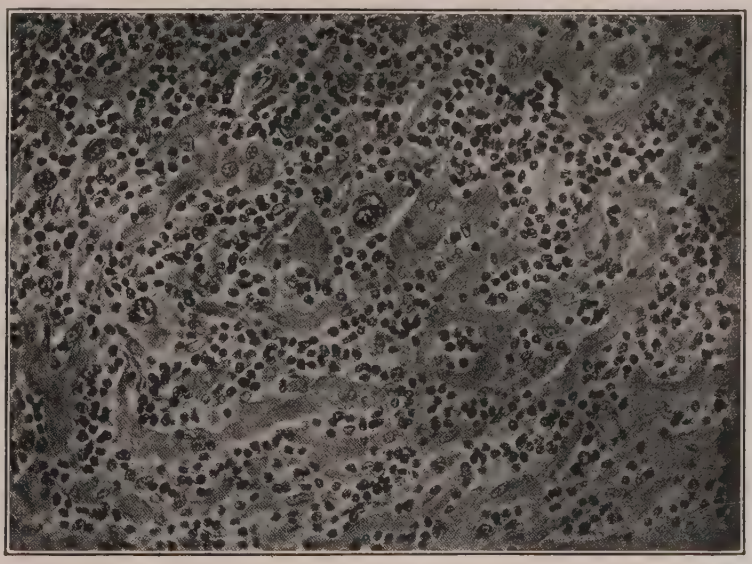


FIG. 322.—LYMPH-NODE IN HODGKIN'S DISEASE.
The trabeculæ have undergone hyaline degeneration. A considerable number of lymphoid cells still remain lying between the connective tissue bands, together with some large cells.

gressive secondary anemia with occasionally a high leucocyte count, though usually the alterations in number and proportions of the white cells from the normal are slight.[1] The tumors are favorably influenced by radium and Roentgen rays, but ultimately the disease is fatal.[2]

It is now generally acknowledged that the tubercle bacillus or organisms resembling it can be demonstrated in only a small percentage of the cases of typical Hodgkin's disease, and repeated efforts to isolate the specific organism, stimulated by the finding by Fraenkel and Much of

[1] Important papers on the histology of Hodgkin's disease, with bibliography, are those by *Longcope*, Bull. Ayer Clin. Laboratory, 1903, No. 1; *Reed*, Johns Hopkins Hosp. Rep., 1902, x, 133 (bibl.); *Simmons, C. C.*, Jour. Med. Research, 1903, N. S. iv, 378, and *Ziegler, K.*, Die Hodgkinsche Krankheit, Jena, 1911 (bibl.).

[2] *Simmons* and *Benet*, Boston Med. and Surg. Jour., 1917, clxxvii, 819.

granular rods resembling bacilli in the antiformin centrifugate obtained from nodes, have recently led to the isolation by Negri and Mieremet[1] of a diphtheroid organism which they call *Corynebacterium granulomatis maligni*. These findings have been confirmed by others.[2] The fact that similar diphtheroid pleomorphic bacteria have been found in carcinomata, in the spleen in Banti's disease, and in diseased lymph-nodes from a variety of conditions, and have been isolated from the blood in various diseases renders necessary most critical studies of the relationships between the newly found organism and Hodgkin's disease, in order to affirm its

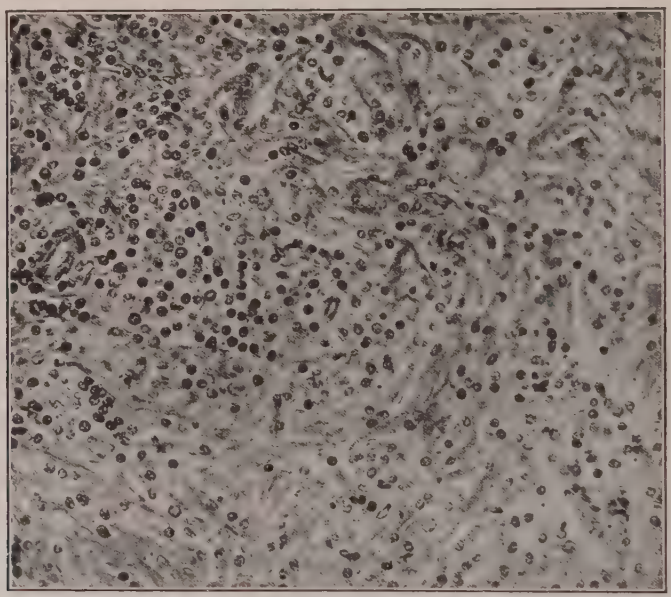


FIG. 323.—LYMPH-NODE IN HODGKIN'S DISEASE, DENSELY FIBROUS.
The lymphoid structures have been almost entirely replaced by connective tissue.

etiological importance. It is at present not considered by most pathologists to be related to the disease.[3] Recently opinion has reverted toward the older view that an attenuated form of tubercle bacillus is responsible for the lesion based on the production of tuberculosis in guinea pigs by the inoculation of Hodgkin's material.[4] Perhaps the disease will ultimately be shown to have several causative agents.

While the infectious nature of Hodgkin's disease is generally accepted, a few pathologists believe that the process is neoplastic.[5]

[1] *Negri* and *Mieremet*, Centralbl. f. Bakteriol., I. Abt. Orig., 1913, lxviii, 292.

[2] *Bunting* and *Yates*, Arch. Int. Med., 1913, xii, 236, and Jour. Am. Med. Assn., 1913, lxi, 1803; 1914, lxii, 516; *Verploegh*, *Kehrer*, and *v. Hoogenhuyze*, München. med. Wchnschr. 1914, lxi, 1158.

[3] *Simmons* and *Benet*, Boston Med. and Surg. Jour., 1917, clxxvii, 819.

[4] *Vasiliu* and *Goia*, Ann. d'anatomie pathologique, 1927, iv, 33 (bibl.); *Lichtenstein*, *A.*, Frankf. Zeit. f. Path., 1921, xxiv, 527. Erganzungsheft (bibl.).

[5] *Mallory*, *F. B.*, Principles of Pathologic Histology, Philadelphia, 1914. For a recent review of the lesions of the disease, see *Beifeld*, *A. F.*, Am. Jour. Med. Sc., 1918, clv, 409.

TUMORS.

Fibroma, myxoma, and **chondroma** have been described as occurring in the lymph-nodes in a few instances. The presence of cartilage is probably due to some congenital displacement rather than to true tumor formation. **Endotheliomata** of the lymph-nodes have been described (Fig. 324),[1] but probably most if not all of these tumors should be considered as sarcomata. Some of the reported cases are unquestionably secondary carcinomata.

The most frequent tumor of the lymph-nodes is the **lymphosarcoma.** This may arise in the lymphatic tissue in any portion of the body, or in

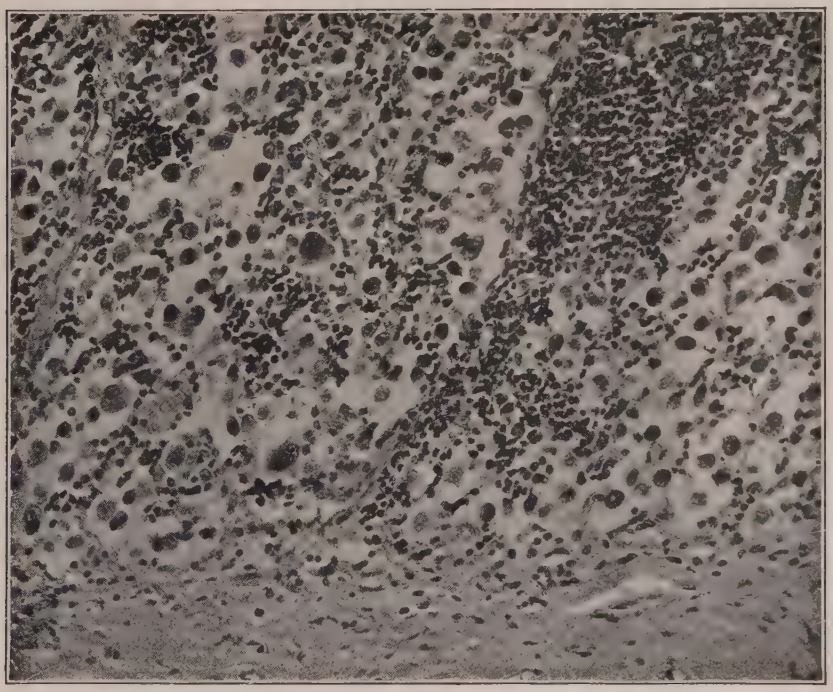


FIG. 324.—SARCOMA OF LYMPH-NODE (ENDOTHELIOMA).

separate lymph-nodes, which rapidly break through the capsule and involve the surrounding tissue, or may begin diffusely, occupying a series of lymph-nodes simultaneously. As has been suggested in the discussion of the lymphomata, the chief point of difference between the benign and the malignant tumors of the lymph-nodes lies in the invasive growth of the latter. Macroscopically, the lymphosarcomata are soft, pale, and occasionally hemorrhagic, though in the slower growing forms sufficient increase in the connective tissue may produce a fairly firm tumor. Microscopically, the diagnosis is occasionally exceedingly difficult. Important

[1] *Wood, F. C.*, Proc. New York Path. Soc., 1912, xii, 54.

facts pointing to malignancy are the large size of the cells, which considerably exceed the normal lymphocyte, the larger nuclei, mitoses, disappearance of the normal architecture of the node, irregularities in sizes and shapes of the individual cells. Cases will be met with in which the final decision as to malignancy must be made on the clinical course. At the onset the blood is usually normal, but an anemia rapidly develops, and in rare instances a considerable number of lymphocytes may appear in the blood. Very rarely **spindle-cell, melanotic,** or **large round-cell sarcomata** arise in the nodes.

Secondary involvement of the lymph-nodes is very frequent. Sarcomata, especially of the melanotic type, may form metastases in the nodes, but in the vast majority of instances secondary tumors are of epithelial origin. When the cells of malignant tumors perforate into the lymph-channels, they may be carried away in the lymph-current aided by the massage given by muscular movements, while possibly the ameboid capacity of the cells of the tumors may aid further in transport. The lymph-channels enter the perifollicular sinuses and the first invasion of the tumor cells is to be noted at this portion of the node. A very slight reaction may be set up by the epithelial cells, or they may remain quiescent in a node for a long period of years, finally to begin again their malignant proliferation; but the usual course is a progressive multiplication of the cells with enlargement of the node into a firm, white, opaque mass which permits easy recognition, even in a fresh specimen. In the later stages, the tumor cells involve the tissue around the capsule of the node, grow into the neighboring vessels, and are distributed throughout the body, producing a generalized carcinosis.

Care should be taken to distinguish between chronic inflammatory hyperplasia of the reticulo-endothelial cells of the lymph sinuses and the invasion by carcinoma, and to remember that occasionally small glands or duct-like cylindrical tubules lined with epithelium are found in the lymph-nodes. Such nodes are most frequent in the pelvis, but may also occur in the neck especially near the salivary glands and in the axillary, inguinal, mesenteric and omental tissues. Such glands probably represent embryonal epithelial remnants.[1]

PARASITES.

Aside from the various forms of **bacteria** which are not infrequently found in the lymph-nodes in infectious diseases, the animal parasites **filaria, trichinella, echinococcus** and **pentastoma** have been described.

[1] *Lüthy, F.*, Virchows Arch., 1924, ccl, 30 (very complete bibl.).

CHAPTER III.

THE SPLEEN AND THYMUS.

The Spleen.

General Characteristics of the Spleen.

In studying the lesions of the spleen it is important to bear in mind the peculiar relations in which this organ stands to the blood-vessels and to the circulation. After passing through the various branches of the splenic artery and the limited systems of capillaries which are associated with it, the blood is not received at once into venous trunks, as in other parts of the body, but is poured directly into the pulp tissue. In this it circulates, under conditions which render it liable to stagnation and undue accumulation, before it is taken again into well-defined vessels through the open walls of the cavernous veins. Moreover, these conditions, naturally unfavorable to undisturbed and vigorous circulation, are reinforced by the association of the splenic with the sluggish and often interrupted portal circulation. Bearing these considerations in mind, it is in a measure plain why, as is in fact the case, the spleen should be more liable to alterations in size than any other organ in the body, and why, serving as it does as a sort of blood filter, it should be especially susceptible to the influence of deleterious materials of various kinds which in one way or another gain access to the blood. The relationship between the lymph-vessels and the spleen is also intimate. Plexiform lymph-sinuses, which partly form actual cavities and partly consist of a spongy meshwork of capillaries in the connective tissue reticulum, connect with the larger cavities and drain into the arteries and veins. The efferent lymph-vessels of the spleen pour out their contents into the sinuses, but there are no afferent or efferent trunks leading to the organ or carrying lymph from it.[1] Finally, the spleen, as an organ which destroys the red corpuscles and may under certain circumstances act as a depot for myeloid tissue, bears an important relationship to many abnormal conditions in the body. It may also contribute lymphocytes to the blood stream.[2]

Malformations and Displacements.

The spleen may be *absent* in acephalous monsters, and with defective development of other abdominal viscera. Absence of the spleen in otherwise normally developed individuals has been recorded. There may in this condition be a compensatory hyperplasia of the lymphatic tissues of the body.[3] The removal of the spleen in adults has only a transitory effect on the number of red and white cells in the blood.[4] Small *accessory spleens*, from the size of a hazlenut to that of a walnut, are not infrequent. They usually lie close to the spleen, but may be at a considerable distance from it; thus they have been found embedded in the head of the pancreas.[5] *Two spleens* of about equal size have been observed. The spleen may be made up of several distinct lobes. It may be *displaced* congenitally or as the result of disease. It may be on the

[1] *Weidenreich*, Arch. f. mikros. Anat., 1901, lviii, 247.

[2] For extensive experimental studies on the spleen and its functions, see *Pearce*, *Krumbhaar*, and *Frazier*, The Spleen and Anæmia, Philadelphia, 1918.

[3] See *Hodenpyl*, Med. Rec., 1898, liv, 695 (bibl.). For a study of the effect of splenectomy in animals on the hemolymph-nodes, see *Warthin*, Vaughan Anniversary Contributions, 1903, p. 216. For certain pathological relations of the spleen, see *Eppinger*, *H.*, Berl. klin Wchnschr., 1913, lii, 1509.

[4] *Paton*, *Gulland*, and *Fowler*, Jour. Physiol., 1902, xxviii, 83.

[5] Hemolymph-nodes may be mistaken for accessory spleens.

right side in transposition of the viscera. As the result of congenital defects in the diaphragm the spleen may be found in the thorax; or in deficient closure of the abdominal wall it may, together with other abdominal viscera, be found outside of the body.

The spleen may be pressed downward by any increase in the contents of the thorax. It may be bound by adhesions to the concave surface of the diaphragm, so that its long axis is nearly horizontal instead of vertical. It may be displaced by changes in the contents of the abdominal cavity. If the organ be increased in size it frequently becomes tilted, so that its lower border reaches the right iliac region. If the ligaments be too long congenitally, or if they are lengthened by traction, and if the organ is at the same time increased in weight, it may become very movable. It may sink downward, with its hilus turned upward; or it may be rotated on its axis, and, owing to torsion of the vessels thus produced, the organ may atrophy; or the pressure of the ligaments and vessels across the duodenum may cause occlusion of the gut.

WOUNDS, RUPTURE, AND HEMORRHAGE.

Wounds of the spleen are usually accompanied by extensive hemorrhage and are commonly fatal. Death usually occurs as the result of this hemorrhage, but it may be due to secondary inflammatory changes. Healing and recovery may, however, occur.

Rupture of the spleen may be traumatic or spontaneous. In the former case it may be due to direct violence in the region of the organ or to injury to the thorax, falls, etc. In certain diseased conditions the spleen is more liable to rupture than when it is normal. The rupture usually involves not only the capsule, but a more or less considerable portion of the parenchyma, and of course leads to hemorrhage. Spontaneous rupture is rare, but may occur in excessive enlargement of the organ, as in typhoid fever, malaria, etc.—see below—or as the result of abscess.

Hemorrhage.—Aside from the extensive hemorrhages from injury and rupture, the spleen may be the seat of small circumscribed hemorrhages in various infectious diseases, although, owing to the peculiar distribution of the blood, it is often very difficult to distinguish between a moderate interstitial hemorrhage and hyperemia. Sacculated aneurysm of the splenic artery has been reported.

ATROPHY.

Atrophy of the spleen may occur in old age; as a result of prolonged cachexiæ, and in connection with profound and persistent anemia; or, more rarely, from unknown causes. The capsule may be wrinkled and thickened, the color pale, the trabeculæ prominent, the consistence increased. The change is largely in the pulp, whose parenchyma cells are decreased in number.

DEGENERATION.

Amyloid Degeneration.—This may affect the Malpighian follicles or the pulp tissue, or both together. When it is confined to the follicles the spleen may or may not be enlarged, and the cut surface more or less

abundantly sprinkled with round or elongated, translucent bodies resembling considerably in general appearance the grains of boiled sago. These are the waxy glomeruli. Such a spleen is often called "sago spleen" (Fig. 325). Microscopical examination shows that the degeneration is confined to the walls of the arteries, capillaries, and reticulum of the glomeruli, with atrophy and often finally total disappearance of the lymphoid cells.

In other cases, either with or without involvement of the follicles, there is waxy degeneration of the blood-vessels and reticulum of the pulp, which may occur in patches or be general and more or less excessive. If the alteration is general and considerable, the spleen is enlarged, its edges are rounded, its consistence is increased. On section it appears

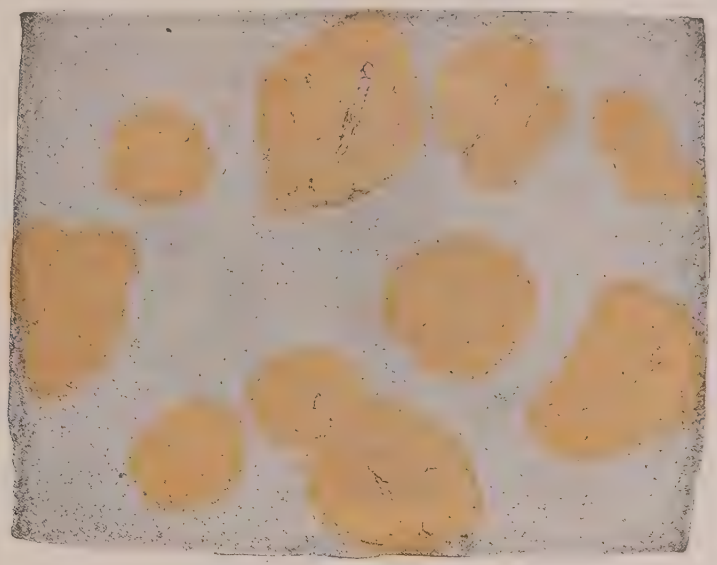


FIG. 325.—AMYLOID DEGENERATION OF THE GLOMERULI OF THE SPLEEN—"SAGO SPLEEN." The waxy portions are stained.

translucent, and the distribution of the degenerated areas may be readily seen when a thin slice is held up to the light. The spleen alone may be affected, or there may be similar degenerations in other organs.

PIGMENTATION.

This may occur as the result of the decomposition of hemoglobin in the organ or elsewhere, under a great variety of conditions: thus after hemorrhagic infarctions, small multiple hemorrhages, acute hyperplastic splenitis, and in hemochromatosis, etc. Or the pigment may be anthracotic and be brought to the organs from the lungs or bronchial nodes; bile pigment also may be deposited in the spleen in jaundice. The pigment may lie in the walls of the smaller arteries, in the cells and

reticulum of the pulp, or free in the latter tissue, or in the follicles. It is usually quite unevenly distributed. The pigment may be red, brown, or black. Anthracotic pigment is deposited especially along the adventitial sheaths of the arteries. It may be sometimes seen with the naked eye in the periphery of the glomeruli as dark crescents. This pigment, derived from the lungs, has gained access to the blood-vessels, through which it is brought to the spleen.

DISTURBANCES OF THE CIRCULATION.

Anemia.—This may be associated with general anemia, but it is not always present in this condition. When it is marked and unassociated with other lesions the spleen may be diminished in size, the capsule more or less wrinkled, the cut surface dry and lighter in color than normal, the trabeculæ unduly prominent.

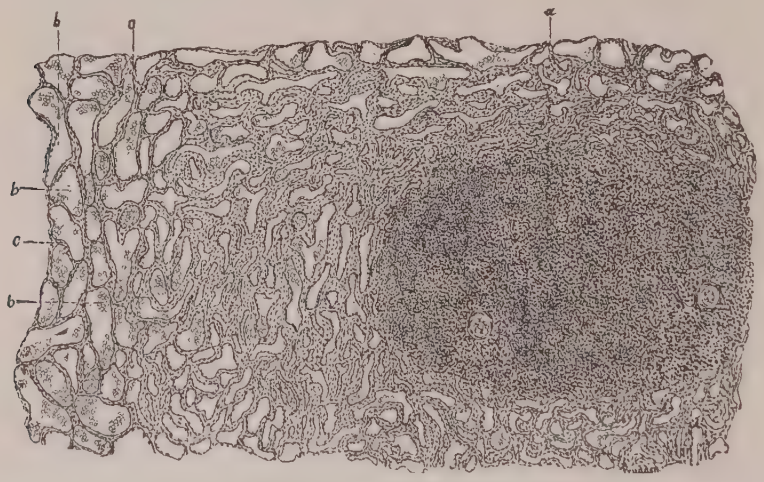


FIG. 326.—HYPEREMIA—CONGESTION—OF THE SPLEEN.

a, Malpighian follicle; *b*, dilated cavernous veins; *c*, trabeculæ of pulp tissue compressed between dilated cavernous veins.

In this, as in other alterations simply of the blood content of the spleen, neither the gross nor microscopical appearances are constant, because of the redistribution of blood which is apt to occur in the viscera after death.

Hyperemia.—PASSIVE HYPEREMIA may occur in obstruction to the portal circulation, most frequently in cirrhosis of the liver, but also with certain valvular lesions of the heart, emphysema, etc. The spleen is enlarged, but usually only to a moderate degree. The capsule is apt to be tense, and on section the pulp is dark red and may be soft or firm. The cavernous veins are dilated (Fig. 326). Usually, when the lesion has existed for some time, there is a thickening of the trabeculæ and reticular framework of the spleen, so that these are prominent on section. In other words, there is a chronic interstitial splenitis following the chronic congestion.

Active hyperemia of the spleen, which in most cases is scarcely to be differentiated from some forms of acute inflammation, and probably in many cases is associated with it, very frequently occurs in a great variety of acute and infectious diseases, such as typhoid fever, pneumonia, diphtheria, pyemia, the exanthemata, etc. The spleen is enlarged, the capsule tense; on section the pulp is soft, dark red in color, often swelling out from the cut surface and concealing the follicles and trabeculæ. Under these conditions the cavernous veins are distended with blood and the interstices of the pulp infiltrated with a variable, sometimes large quantity of red and white blood-cells. Or, in addition to this, there may be hyperplasia (see below).

Embolism and Infarction of the Spleen.—*Embolic infarcts* of the spleen are of frequent occurrence. They may be single or multiple, small or very large, sometimes occupying half of the organ. They usually arise from the detachment of thrombi from the aorta or the heart valves.

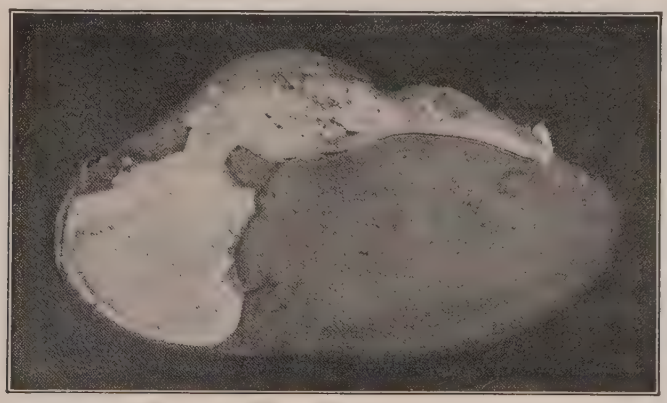


Fig. 327.—Infarction of the Spleen.
Embolus from heart valve in chronic endocarditis.

They are in general approximately wedge-shaped, corresponding to the area of tissue supplied by the occluded artery (Fig. 12, p. 41). They may be hemorrhagic, *i.e.*, red, or they may be white. Infarctions, originally red, may become white after a time from changes in the blood pigment (Fig. 327). They may usually be seen as dark red, reddish white, or white, hard, sometimes slightly projecting areas on the surface of the organ. Not infrequently the center of the infarction is light in color, while the peripheral zone is dark red. A layer of fresh fibrin is sometimes seen over the surface of the infarction. The general as well as the microscopical appearances which they present depend largely upon the age of the infarctions. In the earlier stages the hemorrhagic infarctions present under the microscope little more than a compact mass of red blood-cells, among which may be seen the compressed parenchyma. The white infarction may show at first an outline of the splenic structure, but the entire tissue may be in a condition of coagulation

necrosis. The tissue may disintegrate and soften, and be more or less completely absorbed, with or without fatty degeneration. A zone of inflammatory tissue may appear around the infarction and upon the capsule, and this tissue, becoming denser, may assume the characters of a cicatrix and contract around the unabsorbed remnant of the infarction, so that finally nothing may be left but a dense mass of fibrous tissue, which frequently draws in the surface, causing more or less distortion of the organ. This cicatrix may be pigmented or white.

If the embolus be infective, in addition to its mechanical effects there may be suppuration, gangrene, and the formation of an abscess. There may be perforation of the capsule and fatal peritonitis. Infarctions of the spleen may follow *thrombosis* of the splenic vein.

Thrombosis of the splenic vein is rare as a primary lesion, but it may be of secondary occurrence in connection with portal or mesenteric thrombosis, with other lesions of the spleen, or with acute inflammation of the pancreas. Thrombosis of the splenic vein has been reported following typhoid fever.

INFLAMMATION.

Inflammatory Hyperplasia (*Acute Hyperplastic Splenitis, Acute Splenic Tumor*).—The conditions under which hyperplasia and acute inflammation of the spleen occur have already been mentioned under active hyperemia, with which it is usually associated. It is a frequent though not a constant accompaniment of the acute infectious diseases. The spleen is enlarged, sometimes to two or three times its normal size. On section the pulp is soft, often almost diffluent, and projects upon the cut surface. The color is sometimes dark red, sometimes grayish red, or mottled red and gray. The trabeculæ and Malpighian follicles are usually concealed by the swollen and softened pulp, but the Malpighian follicles are sometimes very prominent.

Microscopical examination shows the marked increase in size to be due in part to the hyperemia; in part to a swelling and increase in the number of cells, sometimes of the pulp, sometimes of the glomeruli, or of both. There are multinuclear cells; cells resembling the ovoid and polyhedral cells of the pulp, but larger and with evident division of the nuclei. Cells resembling leucocytes may be present in large numbers, and larger and smaller cells in a condition of fatty degeneration, or containing pigment, are often seen. The elongated cells lining the cavernous veins may be swollen or increased in number. Not infrequently the larger and smaller cells contain red blood-cells or their fragments. In some cases, particularly in scarlatina, hyperplasia of the follicles is a prominent feature; in other cases, particularly in typhus and recurrent fevers, the cells of the follicles undergo marked degenerative changes, so that they may form small softened areas looking like little abscesses. Focal necroses and areas of small-cell accumulation or cell proliferation are common in typhoid fever and other infectious diseases (see page 238). As the primary disease runs its course the swelling of the

spleen subsides, the capsule appears wrinkled, the color becomes lighter, and sometimes the organ remains for a long time, or permanently, small and soft.

The lesions of the spleen are in many cases due to the presence of microorganisms which are usually present in the spleen in septicemia, or they may be due to soluble toxic substances in the blood.[1]

Suppurative Splenitis (*Splenic Abscess*).—Small abscesses may be found in the spleen as the result of minute infectious emboli, and these may coalesce to form larger abscesses. Sometimes the entire parenchyma is converted into a soft, necrotic, purulent mass surrounded by the capsule. It is rare for simple infarctions to result in abscess. Abscess of the spleen may occur from the propagation of a suppurative inflammation to the organ from adjacent parts; from perinephritic abscesses, ulcer and carcinoma of the stomach, etc. They may open into the peritoneal cavity, inducing fatal peritonitis, or, owing to an adhesive inflammation, the opening may occur into the post-peritoneal tissue, into the pleural cavity, lung, stomach, intestines; or they may open on the surface. On the other hand, the contents of the abscess may dry, shrink, and become encapsulated and calcified. Abscesses may occur in ulcerative endocarditis, pyemia, typhoid fever, and, more rarely, in intermittent fever, and under a variety of other conditions.

Chronic Indurative Splenitis (*Chronic Splenic Tumor*).—There may be, as we have already seen, a new formation of connective tissue in the spleen as a result of chronic congestion or infarctions, or about abscesses. But there is a more diffuse formation of connective tissue, usually in the nature of a hyperplasia, which occurs under a variety of conditions, and is now marked and extensive, and again comparatively ill-defined. It is always associated with more or less extensive changes in the parenchyma. In its most marked form it is found in chronic malarial poisoning; and under these conditions it may be found not only in persons who have suffered from repeated attacks of intermittent fever, but also in those who have not thus suffered but have resided in malarial regions. and presumably had malaria in masked form. The enlarged spleen is often called "ague cake." Similar conditions, though usually less marked, may occur in congenital and acquired syphilis, from prolonged typhoid fever, and as a result of acute hyperplastic splenitis from various causes, and also in leukemia and pseudoleukemia.

The gross appearance of the spleen in chronic indurative splenitis varies greatly, both in the size of the organ and in the appearance of the section. The spleen may be enormously enlarged or it may be of about normal size. It is usually enlarged, however. The capsule is commonly more or less, sometimes unevenly, thickened. The consistence is as a rule, considerably increased, but this is not always the case. The color and appearance of the cut surface present much variation. It may be nearly normal or it may be grayish, or dark brown, or nearly black. The color may be uniform or the surface may be mottled. The folli-

[1] For a study of the rôle of the spleen in infections, see *Courmont* and *Duffau*, Arch. de méd exp., 1898, x, 431 (bibl.); and *Smith, Th.*, Jour. Am. Med. Assn., 1917, lxviii, 669, 764.

cles may be scarcely visible or very prominent; the trabeculæ are in some cases nearly concealed by the pulp; in others they are large, prominent, and abundant, so that the surface is crossed in all directions by an interlacing network of broader and narrower irregular bands, between which the red or brown or blackish pulp lies.

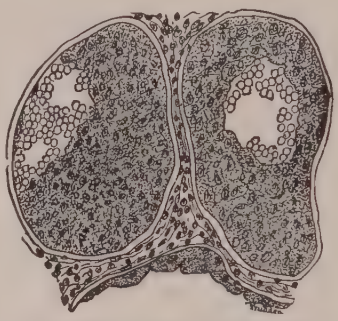


Fig. 328.—Chronic Indurative Splenitis.

Showing swelling and proliferation of the lining cells of the cavernous veins.

Not less varied are the microscopical appearances of the spleen under these conditions. In one class of cases there is more or less uniform hyperplasia of both pulp and interstitial tissue. The parenchyma cells are increased in size and number; there may be swelling and proliferation of the lining cells of the cavernous veins (Fig. 328). The reticulum of the pulp, as well as that of the follicles, and also of the trabeculæ, is thickened. In another class of cases the thickening of the reticular and trabecular tissue, either uniformly or in patches, is the prominent feature (Fig. 329), while the changes in the pulp are rather secondary and atrophic. In both forms irregular pigmentation is frequent, the pigment particles being deposited either in the cells of the pulp or glomeruli, or in the new-formed inter-

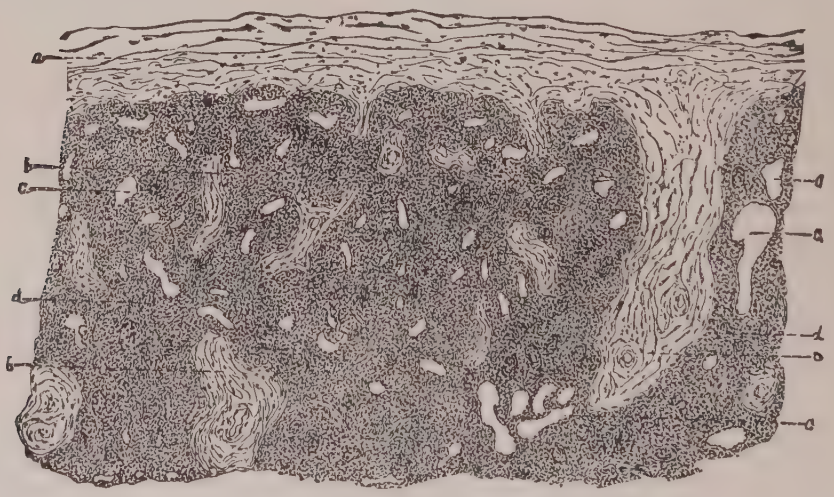


Fig. 329.—Chronic Interstitial Splenitis.

a, Thickened capsule; *b*, thickened trabeculæ; *c*, dilated cavernous veins; *d*, dense pulp tissue with obliterated cavernous veins.

stitial tissue (Fig. 330). Finally, there are all intermediate forms of induration between those described, and the changes are by no means uniform in the same organ. When these spleens are large they are liable to displacement.

Syphilitic Splenitis.—This lesion may present itself as an indurative process due to the formation of new connective tissue, and present no distinct morphological characteristics. In rare cases, however, gummata may be present in connection with the new fibrous tissue; then the nature of the lesion is evident.

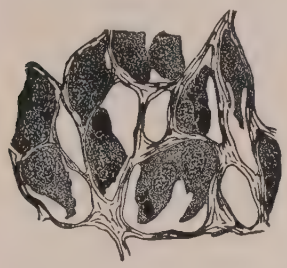


FIG. 330.—MALARIAL SPLEEN.
Showing thickening of the trabecular network of the pulp, with pigmentation of the pulp cells.

Tuberculous Splenitis.—This lesion is usually secondary to tuberculous inflammation in some other part of the body, or is the result of the general infection in acute general miliary tuberculosis. The tubercles may be very numerous and still invisible to the naked eye, or they may be just visible, or as large as a pin's head, and very thickly strewn through the organ or sparsely scattered. In other cases the tubercles are larger, sometimes as large as a pea (Fig. 331), and they are then ordinarily not numerous. Microscopically, they present the usual variety of structure, sometimes as simple tubercle granula, sometimes as conglomerate tubercles; they may consist simply of a collection of small spheroidal cells, or there may be larger polyhedral cells and giant cells with a well-defined reticulum. Cheesy degeneration occurs under the usual conditions. Tubercle bacilli are commonly pre-

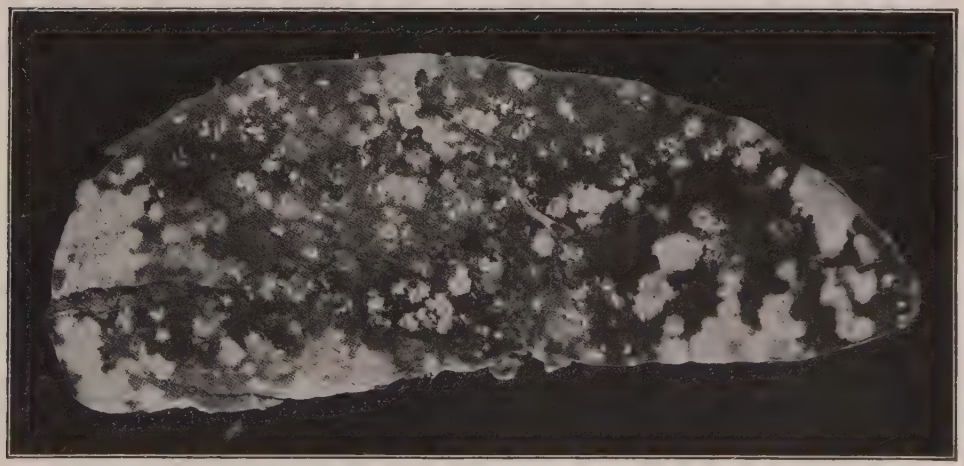


FIG. 331.—TUBERCULOSIS OF THE SPLEEN.
The tubercles are large and irregular in shape and distribution, and are in places confluent.

sent, particularly in the more acute forms, sometimes in small, sometimes in enormous numbers. They seem to be especially abundant in acute general miliary tuberculosis of children. These tubercles may be formed in the glomeruli, in the walls of the smaller arteries, in the pulp tissue, and in the trabeculæ and capsule. Owing to the peculiar

character of the spleen tissue the earlier stages are not readily recognized, since simple collections of small spheroidal cells are not distinctly outlined against the normal tissue. There is frequently a moderate swelling of the spleen, owing to hyperemia and hyperplasia of the parenchyma.[1]

Perisplenitis.—ACUTE INFLAMMATION of the capsule of the spleen may occur as a part of a general or localized peritonitis, or as a result of lesions of the spleen itself, such as infarctions, abscesses, and acute hyperplastic inflammation. Under these conditions a fibrinous pellicle, with more or less pus, may be formed on the surface of the organ. CHRONIC INFLAMMATION, resulting in the production of new connective tissue, either in patches or as a more or less general thickening of the capsule, is of frequent occurrence. It may follow acute inflammation of the capsule, or be a part of general or localized chronic peritonitis. It is common in connection with chronic indurative splenitis, and it may occur from unknown causes. Sometimes the capsule is three or four millimeters in thickness over a considerable area; sometimes very small nodular thickenings or papillary projections occur. As a result of this process, adhesions, sometimes very extensive, may form between the spleen and adjacent parts. The thickened capsule is sometimes more or less extensively calcified.

HEMOLYTIC ICTERUS.

There is a type of jaundice accompanied by enlargement of the spleen which is apparently hereditary, as it occurs in families through a number of generations. The disease is found in persons who are otherwise in good health and who often live to old age. The symptoms occur in attacks, the patient suffering from chills or fever, with headache, general muscular pain, and jaundice. Bile is usually present in the blood, may or may not be present in the stools, and is rarely found in the urine. During the crisis the spleen enlarges. The attacks last for a few weeks, though often the patients are continuously slightly jaundiced. When bile is absent during the attacks, urobilinogen and urobilin are abundant (58 per cent., Giffin) in the urine. Gall-stones are not infrequently found in the gall-bladder and in the ducts. Their formation probably depends upon the excretion of large quantities of thick bile from which cholesterin separates in the gall-bladder. Removal of the stones does not cure the jaundice, but remarkably good therapeutic results have been obtained by splenectomy.[2]

The blood shows a moderate anemia and during the attack the red cells are polychromatophilic; normoblasts are often present; and large numbers of cells with reticulations appear. Autoagglutination of the red cells may be demonstrated in some instances. These blood changes

[1] For study of tuberculosis of spleen, with bibl., see *Winternitz, M. C.*, Arch. Int. Med., 1912, ix, 680. For a case of splenic tuberculosis with polycythemia, see *Douglas, J.*, and *Eisenbrey, A. B.*, Am. Jour. Med. Sc., 1914, cxlvii, 479.

[2] *Elliott, C. A.*, and *Kanavel, A. B.*, Surg., Gynec., and Obst., 1915, xxi, 37 (good bibl.); *Giffin, H. Z.*, ibid., 1917, xxv, 152; *Peck, C. H.*, Jour. Am. Med. Assn., 1916, lxvii, 788; *Friedman, G. A.*, and *Katz, E.*, Jour. Am. Med. Assn., 1916, lxvii, 1295.

disappear when the jaundice ceases. A striking phenomenon in the blood is the great increase in the fragility of the red corpuscles when tested by suspension in sodium chloride solutions. Normal blood begins to hemolyze in a solution containing 0.44 per cent. of sodium chloride, and hemolysis is complete in a 0.28 per cent. solution. In these jaundiced patients, the blood begins to hemolyze as a rule in 0.5 to 0.55 per cent. solutions, and complete hemolysis is frequently observed in a 0.35 per cent., but may be produced even in a 0.4 per cent. solution. Exceptionally hemolysis may occur in a 0.7 per cent. solution. After operation this fragility may diminish somewhat and even disappear, but usually it remains for a long time.

The cause of the disease is unknown; but it is presumably due to some hemolytic agent set free during the crisis or possibly to a congenital feebleness of the red cells; and the enlargement of the spleen may be caused entirely by the increased blood destruction.

Another type of the disease is not hereditary, but appears spontaneously, though in its clinical symptoms it does not differ from the familiar type.

The findings at autopsy are very slight. The spleen is large; the follicles are poorly marked; large numbers of red cells lie in the pulp and there is often dilatation of the sinuses and swelling of the endothelium. Usually there is a considerable deposit of iron-containing pigment in the liver, kidneys, and bone-marrow. Considerable hyperplasia of the latter may be found if the patient dies while the disease is active.

A third form of hemolytic icterus is probably due to infections in persons with substandard blood resistance. The patients may be attacked with an endocarditis or a pneumonia of the lobar, bronchial, or lobular type, suddenly become jaundiced, and show, if the blood be examined, an enormous destruction of the red cells. In these cases the jaundice may be due to the large amount of hemoglobin set free. The spleen is usually not so much enlarged as in the chronic types.[1]

CHRONIC ENDOTHELIAL HYPERPLASIA OF THE SPLEEN. ("Primary Splenomegaly.")

Gaucher described as a primary endothelioma of the spleen a slowly progressive lesion in which the organ is greatly enlarged and firm, presenting numerous irregular white or yellowish areas. The splenic and mesenteric lymph-nodes and the liver are enlarged. Microscopically, the splenic lesion is found to be due chiefly to the presence of large numbers of cells of peculiar type (Fig. 332), with small, deeply staining nuclei and large reticulated cell bodies, highly attractive to eosin. Pigment may or may not be present. The cells line or fill the sinuses of the spleen, and occur in the lymph-nodes (Fig. 333), in the sinusoids of the liver, and in the bone-marrow. They do not contain stainable fat or lipoid. They are probably derived from the cells of the reticulum, possibly also from the

[1] See for general survey of icterus in infectious diseases, *Posselt*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1915, xvii[2], 719; and *Chauffard, A.*, and *Troisier, J.*, Gilbert and Weinberg, Traité du sang, Paris, 1913, i, 227.

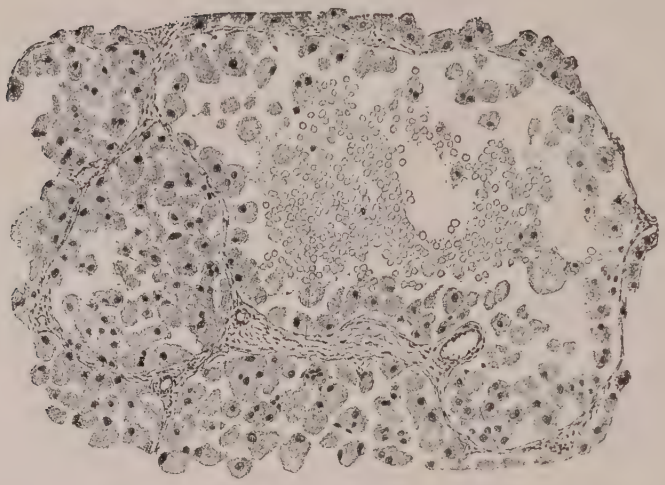


Fig. 332.—Chronic Endothelial Hyperplasia of the Spleen.
Showing increase in number and exfoliation of the endothelium of the cavernous veins.

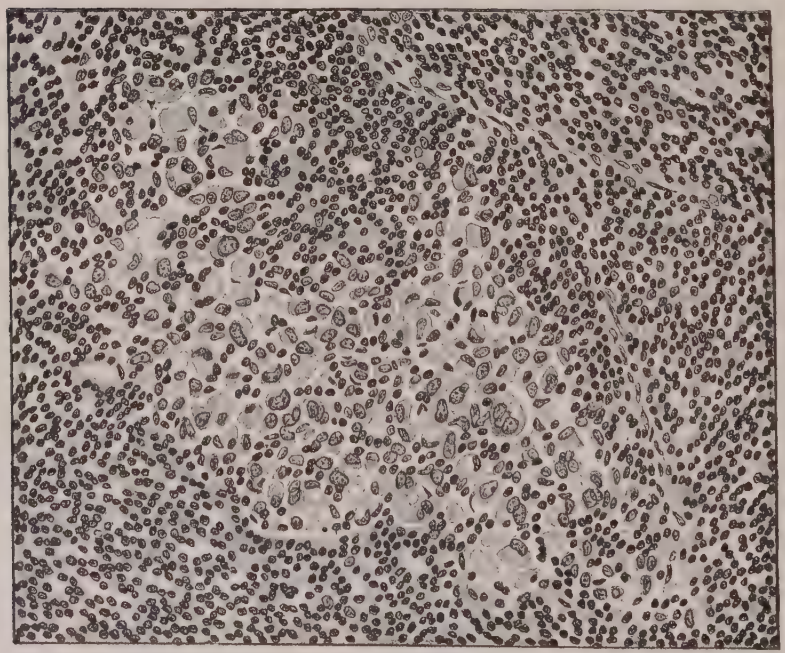


Fig. 333.—Lymph-node from Case of Hyperplasia of Spleen—Gaucher Type.

endothelium of the sinuses. The cause of the disease is unknown; it begins in childhood and frequently affects several members of the family. The patients show anemia, tendency to hemorrhage, and emaciation; but death is usually due to complicating diseases.[1]

Other types of splenomegaly resembling slightly the Gaucher form have been described,[2] but in them the lesion is confined to the endothelium of the capillary walls and does not affect the reticulum cells of the pulp as in the true primary splenomegaly.

ALTERATIONS OF THE SPLEEN IN LEUKEMIA, ANEMIA, AND HODGKIN'S DISEASE.

The lesions of the spleen in leukemia consist in general of a hyperplasia, sometimes most marked in one of the structural elements of the

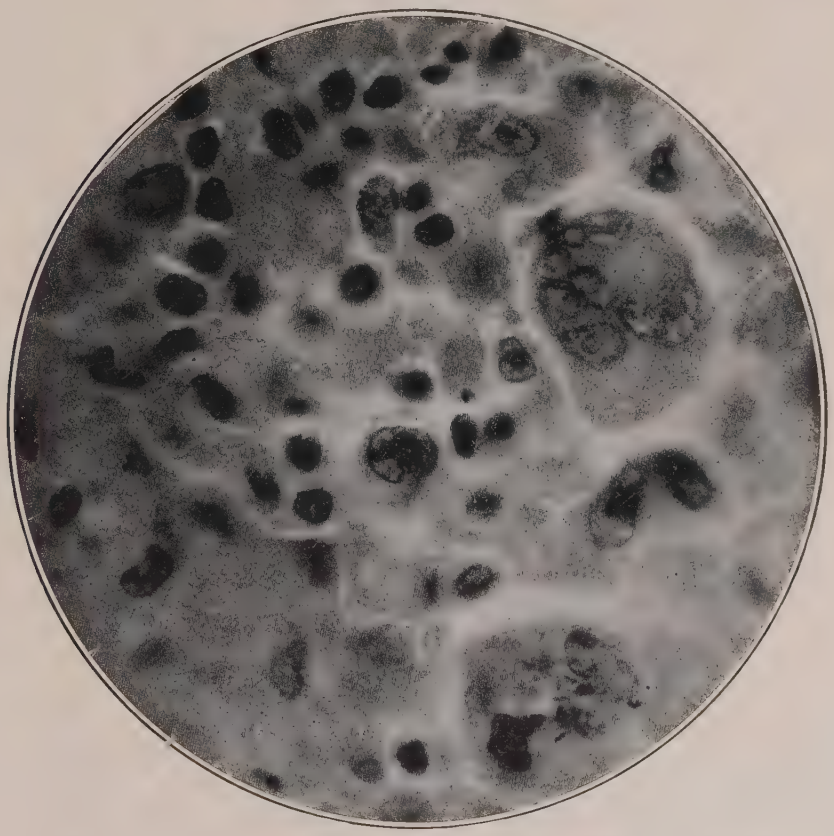


FIG. 334.—HODGKIN'S DISEASE. SHOWING LARGE CELL HYPERPLASIA IN SPLEEN.

organ, sometimes in another, though usually all participate in the alteration. The changes which occur in the earlier stages are but little

[1] For details of this lesion, see *Bovaird, D.*, Am. Jour. Med. Sc., 1900, cxx, 377; *Brill, Mandlebaum,* and *Libman,* ibid., 1905, cxxix, 491; *Brill* and *Mandlebaum,* ibid., 1913, cxlvi, 863; *Mandlebaum, F. S.,* Jour. Exper. Med., 1912, xvi, 979; *Mandlebaum, F. S.,* Am. Jour. Med. Sc., 1919, clvii, 366.

[2] See *Pentmann, I.*, Frankfurt. Ztschr. f. Path., 1916, xviii, 121.

known (Fig. 334). The gross appearances of the spleen vary. It is, as a rule, enlarged and sometimes is ten or fifteen times the normal size. It is commonly hard, but is sometimes of the ordinary consistence, or softer, and the capsule is generally thickened and rough (Fig. 335). The section of the spleen may be of a uniform dark red color, but it is more frequently mottled red and gray. Sometimes the Malpighian follicles are inconspicuous, but they are very often enlarged and prominent. They may be two to four millimeters in diameter, and, owing to an infiltration of the arterial sheaths with lymphocytes, may appear to the

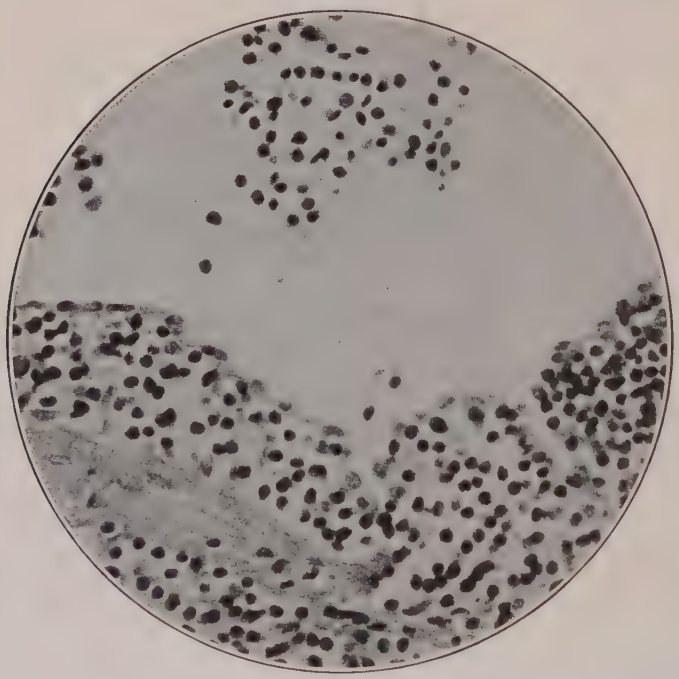


Fig. 335.—Subendothelial Infiltration of Splenic Sinuses by Lymphoid Cells in a Case of Lymphatic Leukemia.
A similar lesion occurs in Hodgkin's disease.

naked eye as grayish, round or elongated bodies, arranged along branching, interrupted, grayish streaks. The trabeculæ may be greatly thickened, as also the reticulum of the pulp, so as to be evident to the naked eye. Brown or black pigment may be collected around the glomeruli or in the pulp. Hemorrhagic infarctions or circumscribed extravasations of blood may further complicate the picture.

Microscopically, the appearances are essentially the same as those above described in acute hyperplasia and in chronic interstitial splenitis, depending upon the stage and variety of the disease.

In lymphatic leukemia the pulp is largely lymphatic; in the myelogenous form vast numbers of myelocytes are present. In severe anemias,

especially in children, myeloid hyperplasia is frequent but not extensive, and marrow giant cells may be found.

In pernicious anemia phagocytosis of red cells is often, though not always, present. In Hodgkin's disease the characteristic changes may be discrete or very extensive. The morphology is the same as in the nodes. In splenic anemia and in Banti's disease a chronic interstitial process with sinus dilatation is often, though not constantly, present. Owing to the great size which some such spleens attain they are liable to displacement, and they may interfere by pressure with the functions of neighboring organs.

TUMORS.

The spleen is but rarely affected by primary tumors. **Fibromata, chondromata,** and **osteomata** have been seen; **lymphangiomata** are rather more frequent; and **hemangiomata** are not very rare.[1] Cavernous **angioma** has been reported.[2]

Sarcomata[3] of various types have been reported, usually of the spindle-cell or the very vascular form; and the latter have sometimes been incorrectly termed *endotheliomata.*[4]

Secondary tumors also are rare. Lymphosarcoma and melanosarcoma are the most frequent; while carcinomatous nodules are but very rarely seen, the spleen being involved in not over 1 per cent. of the fatal cases. There are two reasons for this: 1, carcinoma is usually spread by the lymphatics, which have no direct connection with the spleen, so that metastatic nodules to reach this organ must pass through the blood-vessels; and 2, the pulsations of the organ make it exceedingly difficult for embolic particles of carcinoma to grow through the endothelium of the sinuses and attach themselves to the tissues.

It has been shown experimentally that the spleen when directly inoculated with carcinoma is just as suitable a soil for the growth of the tumor as is any other portion of the body (see page 389).[5]

Dermoid cysts are described, but are rare. Other larger and smaller cysts, whose mode of origin is in most cases obscure, not infrequently occur; some of these may be lymphangiomata; others are probably hemorrhagic cysts following trauma.[6]

PARASITES.

Pentastoma denticulatum, the larval stage of Linguatula rhinaria, is very rarely found in the spleen. **Cysticercus** is rare. **Echinococcus** is occasionally found, and, if the cysts are large or numerous, may cause more or less extensive atrophy of the organ. **Spirochæte obermeieri** may

[1] *Thiele,* Virchows Arch., 1904, clxxviii, 296.

[2] *Dowd, C. N.,* Ann. Surg., 1915, lxii, 177.

[3] *Bunting,* Univ. Pennsylvania Med. Bull., 1913, xxv, 318 (bibl.); and *Simon,* Beitr. z. klin. Chir. (Bruns), 1902, xxxv, 318 (bibl.).

[4] *Risel,* Zieglers Beitr., 1909, xlvi, 241 (bibl.).

[5] *Goldmann, E. E.,* Beitr. f. klin. Chir. (Bruns), 1911, lxxii, 1.

[6] For studies of cysts of the spleen, see *Wohlwill, F.,* Virchows Arch., 1908, cxciv, 306 (bibl.); and *Schmidt, M. B.,* ibid., 1901, clxiv, 50 (bibl.).

be present in relapsing fever. Leishmania donovani and infantum have been found in the spleen (see page 143). Plasmodium malariæ is often present in enormous numbers. Various forms of bacteria have been found in the spleen, the pyogenic cocci in pyemia, smallpox, ulcerative endocarditis, diphtheria, and under other conditions; the Bacillus anthracis occurs here in anthrax; the Bacillus tuberculosis in tuberculous inflammation; and the Bacillus typhosus in typhoid fever.

Thymus.

ANATOMY AND FUNCTION.

The thymus develops in man as a flattened sac from the third and fourth branchial pouches on each side of the neck, the main portion of the gland being derived from the third. The lumen of the sac becomes obliterated with the growth of the organ, but traces of the original canal may be found. In the fully developed gland the two lobes can be easily made out. Aberrant fragments of thymus have been found in the thyroid and parathyroid and thyroid tissue in the thymus. Microscopically two types of cells are distinguishable, one lymphocytes, the other epithelial cells which form the reticulum of the cortex, the greater part of the medulla and also exist in masses known as Hassal's corpuscles. The thymus reaches its largest size in the early period of life, then undergoes involution or atrophy, losing a considerable proportion of its characteristic cells. In old age it is represented by a mass of fat tissue in which a few lymphocytes and Hassal's bodies may be found. In the newborn[1] the average weight of the gland is about 13 grams. Between first and fifthy ears it is 23 grams; from the sixth to tenth years, 37 grams; and from the tenth to the twentieth years, 25 grams. From this period on it atrophies rapidly, though small portions always remain. The thymus may persist under exceptional conditions until middle age (Fig. 299). Furthermore, it may become enlarged, the so-called hypertrophy of the thymus, which is, however, rather a hyperplasia than a hypertrophy. The new formed tissue may present a more or less marked lobulated or glandular appearance. Such tissue is largely composed of lymphoid cells, or in some instances of larger polyhedral cells, the so-called epitheloid cell.[2]

The function of the thymus is still unknown. The theory that its extirpation induces rickets has been shown to have no foundation.[3] Its excision in young animals has been stated to exert a deleterious effect on the development of the skeleton, the genital apparatus and psychic maturity, but others have found no such influence.[4]

INVOLUTION AND HYPERPLASIA.

A very rapid shrinkage of the thymus gland is seen in acute and chronic wasting diseases, severe infection, after exposure to X-ray, and in starvation. Histologically, the lymphocytes diminish and the Hassal's corpuscles become apparently more abundant. This is probably due to the reduction in the total volume of the gland and not to new formation.[5]

In the condition known as status lymphaticus or status thymicolymphaticus the thymus is often very greatly enlarged. The question whether the symptoms of difficult respiration are produced by pressure of the thymus on the trachea is still under dispute. Also the exact relationship between sudden death and the existence of a large thymus in status lymphaticus is unsettled. The relief of symptoms seen after

[1] For the significance of a persistent thymus in certain cases of sudden death, see *Norton*, Philadelphia, Med. Jour., 1898, i, 249 (bibl.). On the relationship of hyperplasia in a persistent thymus to Hodgkin's disease, consult *Brigidi* and *Piccoli*, Zieglers Beitr., 1894, xvi, 388.

For a study of the weight of the thymus in infancy, see *Bovaird* and *Nicoll*, Arch. Pediat., 1906, xxiii, 641. For a thorough and admirable study of the normal and pathological histology of the thymus, see *Pappenheimer*, A. M., Jour. Med. Research, 1910, N. S., xvii, 1; Jour. Exper. Med., 1914, xix, 319; 1914, xx, 477.

[2] *Lochte*, Centralbl. f. allg. Path. 1899, x, 1 (bibl.).

[3] *Renton* and *Robertson*, Jour. Path. and Bacteriol., 1916, xxi, 1. See also *Matti*, Ergebn. d. inn. Med. u. Kinderheilk., 1913, x, 1; and *Wiesel, J.*, Lubarsch-Ostertag, Ergebn. d. Allg. Path. 1911, xv, 417; *Klose* and *Vogt*, Beitr. z. klin. Chir. (Bruns), 1910, lxix, 1.

[4] *Park* and *McClure*, Jour. Exper. Med., 1917, xxv, 129; Am. Jour. Dis. Chil., 1919, xviii, 317.

[5] *Hammar, J.*, Ergebnisse d. Anat. u. Entwcklngs., 1909, xix, 1.

the excision of such enlarged thymus glands, however, points to the possibility of mechanical pressure being of importance in the production of symptoms. In about three-quarters of the cases of exophthalmic goiter a more or less considerable enlargement of the thymus exists.[1]

Histologically the lesion in the enlarged thymus gland connected with exophthalmic goiter, is a great increase in the lymphoid cells. Such patients are apt to show also a blood lymphocytosis. Hyperplasia of the thymus also occurs in a great proportion of cases of Addison's disease, acromegaly, genital hypoplasia, or eunuchoidism, and also in myasthenia gravis. The exact nature of the correlation between these diseases and thymic enlargement is still undetermined. In animals castration at an early age inhibits the involution of the thymus.

HEMORRHAGE.

Small and sometimes large hemorrhages are occasionally seen in the thymus of young children as the result of venous congestion in asphyxia, poisoning and severe infections. They may also occur in purpura and other hemorrhagic diseases.[2]

INFLAMMATION.

Suppurative inflammation of the thymus is of occasional occurrence, and is usually secondary to a similar inflammatory process in some other part of the body. Tuberculosis is seen in connection with general miliary tuberculosis, and occasionally is found as an extension of tuberculosis of the mediastinal lymph-nodes. Hodgkin's disease may also involve the tissue of the thymus gland. Syphilis of the thymus is very rare,[3] but in a certain proportion of cases of congenital syphilis a peculiar lesion called a Dubois abscess is found. These abscesses consist of sharply bounded areas containing a rather inspissated and firm purulent material. Treponema pallidum has been demonstrated in the material of the abscess.[4]

TUMORS.

Tumors of the thymus are rare. A few examples of angioma, lipoma, myxoma, dermoid and other cysts have been noted. Some of these cysts have been found to be lined with ciliated epithelium, which might be expected from the branchial cleft origin of the thymus gland.[5] Spindle-celled sarcomata have also been described as a great rarity.

The frequent tumor is a neoplasm resembling in some ways a lymphosarcoma, but showing slight differences which sometimes permit a differential diagnosis being made. Occasionally the Hassal's corpuscles also take part in the tumor formation, though not contributing any large bulk of the tumor mass. Usually the cells of the tumor are somewhat larger than the normal lymphocyte and such growths are also apt to contain large, pale cells resembling those seen in Hodgkin's disease. In some instances giant cells of the bone marrow type have been met with. Some hold that many of these tumors represent a peculiar malignant type of Hodgkin's disease, and that the large cells arise from the reticulum of the gland.

[1] *Matti.*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1912, xxiv, 665; also *Capelle*, München. med. Wchnschr., 1908, lv, 1826.

[2] For a study of apoplexy of the thymus, see *Mendelsohn*, Arch. f. Kinderheilk, 1906, xliv, 1; and *Wahl, R. N.*, and *Walthall, D.*, Am. Jour. Dis. Chil., 1922, xxiv, 27 (bibl.).

[3] *Hammar, J. A.*, Zieglers Beitr., 1920, lxvi, 37 and 195.

[4] *Oliver, J.*, Am. Jour. Dis. Chil., 1917, xiii, 158.

[5] *Hueter, C.*, Zieglers Beitr., 1913, lv, 117.

CHAPTER IV.

THE THYROID AND ADRENALS.

The Thyroid.

Malformations.

The thyroid gland is sometimes very small, either as the result of atrophy or as a congenital deficiency.[1]

The thyroid may be irregularly lobulated. There may be small accessory glands situated at some distance from the normal position, as in the tongue, trachea, mediastinum or pleura.[2]

DEGENERATION.

Colloid degeneration of the epithelial cells of the gland, and the filling of the alveoli with colloid material, are of common occurrence, and when in moderate degree may be regarded as normal, since a certain amount of this change is found in many otherwise apparently normal glands. It may occur, however, to such an extent as to constitute an important lesion (see below).

Amyloid degeneration, particularly of the blood-vessels, is of infrequent occurrence.

Hyaline degeneration of the stroma of the thyroid may occur.

DISTURBANCES OF CIRCULATION.

Hyperemia of the thyroid gland, often accompanied by considerable enlargement of the organ, may be the result of valvular disease of the heart; it occurs also in exophthalmic goiter. It may be temporary or permanent, and in the latter case may be associated with the formation of new connective tissue. Hemorrhages may occur, leading to cysts and to pigmentation of the organ.

INFLAMMATION. (Strumitis.)

Inflammation of the thyroid gland is not very common and may occur under a variety of conditions, especially in infectious diseases, septicemia, typhoid fever, diphtheria, etc. It may result in the formation of larger and smaller abscesses or in the production of new connective tissue which may be associated with atrophy of the parenchyma. A pseudotuberculous lesion is occasionally seen, in which the colloid contents of the alveoli set up an active connective tissue reaction with the

[1] For the relationship of this condition to cretinism and myxedema, see page 479.

[2] *Payr. E.*, Arch. f. klin. Chir. (Langenbeck), 1906, lxx, 730.

production of giant cells.[1] This chronic inflammatory lesion has often been mistaken for true tuberculosis (Fig. 336). **Tuberculous inflammation,** with the formation of miliary tubercles, is of infrequent occurrence.[2] **Syphilitic inflammation,** with the formation of gummata, has been described, but is rare.

STRUMA. (Hyperplasia of the Thyroid; Goiter.)

Among the most important of the lesions of the thyroid is the enlargement of the organ commonly known as *goiter* or *struma.* The enlarge-

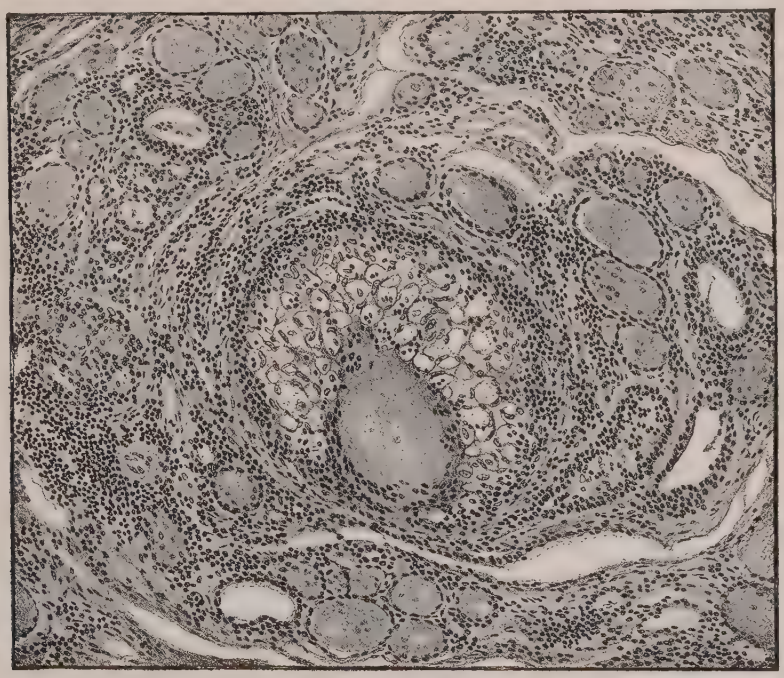


Fig. 336.—Pseudotubercle in Chronic Thyroiditis.
This lesion is frequently mistaken for tuberculosis, but is due to the setting free of the colloid material of the thyroid during the inflammatory process in chronic thyroiditis.

ment of the gland may occur in several ways. Thus, a simple hyperemia may, as above stated, lead to considerable enlargement of the organ, and this is sometimes called *struma hyperæmica.* The true goiter, however, consists in the enlargement of the old and the formation of new gland alveoli, while with these changes there is very frequently associated a greater or less amount of colloid degeneration.[3] When there is

[1] *Wilke,* Virchows Arch., 1913, ccxi, 165.
[2] *Mosiman,* Surg. Gyn. & Obst., 1917, xxiv, 680.
[3] For a study of the normal and pathologic histology of the thyroid, with bibl., see *Erdheim,* Zieglers Beitr., 1903, xxxiii, 159. For myxedema and Basedow's disease see pp. 479 and 482. For relations of thyroid to pregnancy, see *Ward, G. G.,* Surg., Gynec., and Obst., 1909, ix, 617. For relations of thyroid hyperplasia to various diseases and infections, see *Farrant, R.,* Brit. Med. Jour., 1914, i, 470; also *Bircher,* Lubarsch-Ostertag, Ergebn. d. allg. Path., 1911, xv, 82.

new formation of gland tissue the growth has the character of an *adenoma.* The hyperplasia may occur diffusely, so that the whole gland is more or less enlarged; or it may occur in the form of circumscribed nodules. When the colloid degeneration is prominent, so that the tumor has a gelatinous appearance, it is called *colloid struma* (Fig. 337).[1] Accumulations of fluid, blood, colloid, etc., in the old or new-formed alveoli, may lead to dilatation and atrophy of the walls of the alveoli, so that cysts, sometimes of large size, are formed. Thus occurs the *cystic struma.* Again, the blood-vessels may undergo marked dilatation, so that we may have a *telangiectatic struma;* or *cavernous angiomata* may form within

Fig. 337.—Colloid Struma—Goiter.
The colloid material filling the alveoli is stained red.

goiters. Very frequently all these varieties of lesions are present in the same goiter. The appearances may be rendered still more complex by the occurrence of hemorrhage and pigmentation, calcification, purulent or indurative inflammation (strumitis), and by the not very infrequent association with carcinoma and sarcoma. The excitants of goiter are not well understood. The growth is, as a rule, slow, but occasionally a very rapid enlargement occurs as the result of a sudden increase of the colloid degeneration. In many cases even very large goiters give rise to but moderate inconvenience, but they may assume great significance by encroaching upon neighboring parts, especially if the mass or a portion of it lies behind the sternum. Thus death may be caused by pressure on the trachea, esophagus, or on the large vessels.

[1] For a study of the pathological anatomy of the thyroid, see *Marine* and *Lenhart*, Arch. Int. Med., 1911, vii, 506. For a general study of the diseases of the thyroid, see *McCarrison*, The Thyroid Gland in Health and Disease, New York, 1917.

A rare lesion of the thyroid is the so-called Riedel's struma or chronic ligneous thyroiditis. A marked enlargement of one or usually both lobes of the glands is present. The swelling is apt to be symmetrical, is extremely hard, and usually the surface of the gland is smooth, but distinct nodules are occasionally present. The borders of the gland, as a rule, cannot be distinctly made out because of the fibrous adhesions extending from the gland to the vessels, fasciæ, and muscles of the neck. Thus the disease resembles carcinoma of the thyroid clinically. Fever is not present and a normal basal metabolism is usual. The pathological changes are not wholly characteristic as they may occur over very

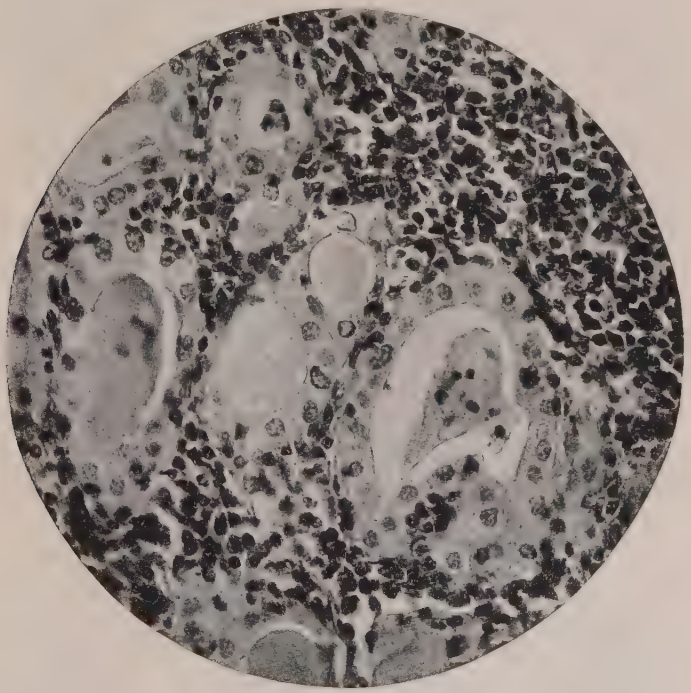


Fig. 338.—Chronic Thyroiditis (Riedel's Struma). Early Case. × 350.

limited areas in ordinary goiter as mentioned above, but when the whole lobe is involved the clinical picture is distinct.

On gross section the tissues are grayish white in color with occasional small yellowish areas representing degenerated tissue. In the early cases the most marked lesion is the extensive lymphocytic infiltration (Fig. 338) of the stroma with the formation of germinal centers (Fig. 339). As this infiltration progresses, the acini of the thyroid diminish in size, the cells undergo hyperplasia, sometimes assume a syncytial form and colloid contents diminish. Invasion of the lumen with leukocytes or phagocytes which digest and absorb the colloid mass is not infrequently seen. As the process continues, a large amount of connective tissue may be formed which replaces the glandular structures (Fig. 340)

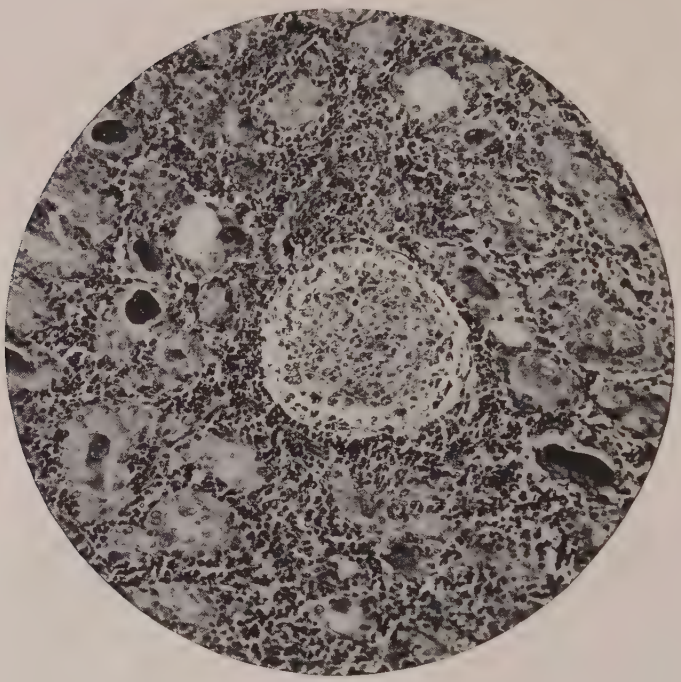


Fig. 339.—Riedel's Struma. Germinal Center in Early Stage. × 140.

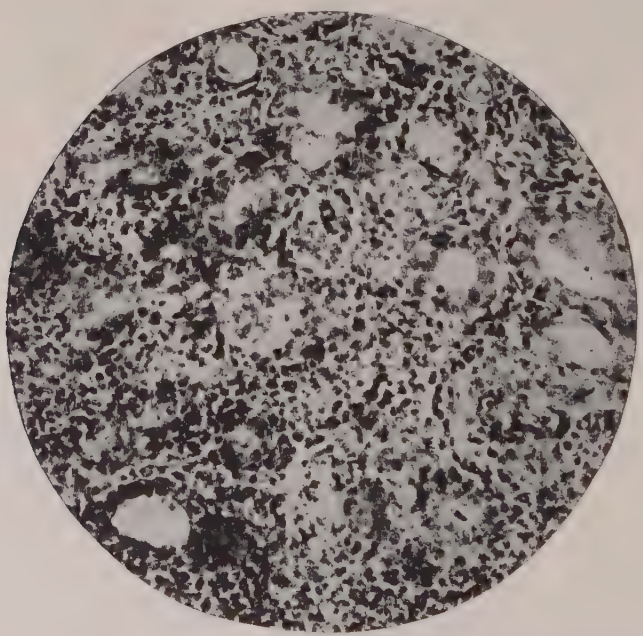


Fig. 340.—Chronic Thyroiditis (Riedel's Struma) Showing Extensive Lymphocytic Infiltration and Atrophy of the Gland Tubules. × 200.

and in the late stages the thyroid structures may be completely replaced with a practically solid mass of dense connective tissue in which may be found small foci of lymphocytes and only occasionally acini. The adjacent lymph nodes may show chronic inflammation. Despite the extensive damage to gland structures, myxedema does not occur. Bacteriological studies have not revealed any coexisting organisms, so that the condition must be considered as a chronic inflammatory process of unknown etiology.[1]

TUMORS.

Adenomata,[2] which are not rare and may be congenital, are either encapsulated or diffuse; in the latter instance, it is often difficult to dis-

FIG. 341.—PAPILLARY ADENOMA OF THYROID.

tinguish between an adenoma and a hyperplasia. *Hemorrhagic cysts* are not uncommon,[3] while cysts of another type sometimes originate in adenomata.[4] *Papillary adenomata* are occasionally found (Fig. 341). The *fetal adenoma,*[5] a very frequent type, consists of solid plugs or alveoli of small epithelial cells (Plate III).

Carcinoma may be either *solid, glandular,* or *papillary,* or may resemble a goiter or even the normal gland,[6] showing its malignant nature

[1] *Shaw* and *Smith,* Brit. Jour. Surg., 1925, xiii, 93; *Meeker, L. H.,* Am. Jour. Path., 1925, i, 57; *Smith* and *Clute,* Am. Jour. Med. Sci., 1926, clxxii, 403.

[2] *Bloodgood,* Surg., Gynec., and Obst., 1906, ii, 121; *Ribbert,* Frankfurt. Ztschr. f. Path., 1915, xviii, 55.

[3] *Bradley,* Jour. Exper. Med., 1896, i, 401.

[4] *Bloodgood,* Surg., Gynec., and Obst., 1905, i, 113.

[5] *Wölfler,* Arch. f. klin. Chir. (Langenbeck), 1833, xxix, 1, 754.

[6] *Gierke,* Third Sci. Report, Imperial Cancer Research Fund, London, 1907, p. 115; Virchows Arch., 1902, clxx, 464; *Oderfeld* and *Steinhaus,* Centralbl. f. allg. Path., 1903, xiv, 84.

in the instance last mentioned only by its clinical behavior. Another peculiarity of carcinoma in the thyroid is that tumors with a morphology which, in other organs, would lead to the diagnosis of carcinoma may exhibit little or no malignancy, and, indeed, may often disappear spontaneously. The so-called *benign metastasizing goiters*[1] (*general thyroid malignancy*) are perhaps more properly to be regarded as carcinomata. The test of malignancy in all these thyroid carcinomata is vascular invasion. The tumor tissue concerned in such invasion may be adenoma-

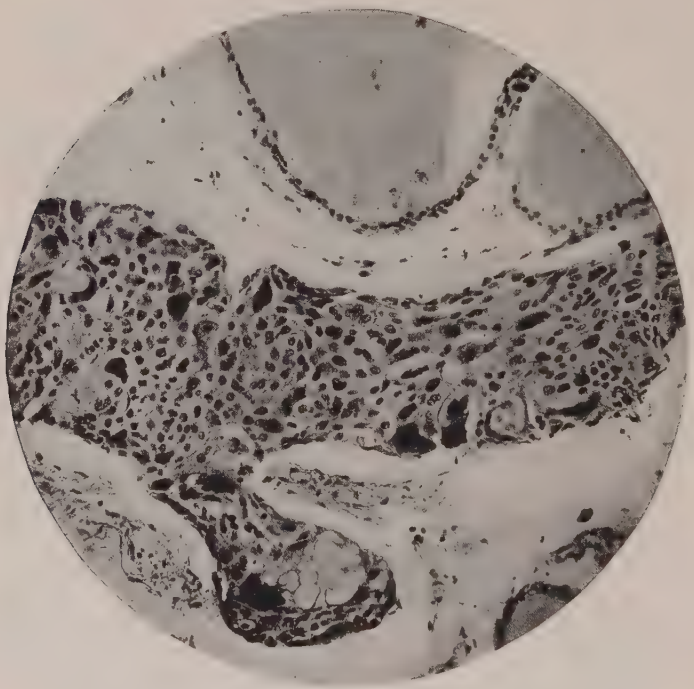


Fig. 342.—Squamous Cell Carcinoma of Thyroid Gland. × 140.

tous in structure or frankly carcinoma; but care must be taken not to be mislead by artifacts due to traumatism of the material. A very rare form of tumor is the *squamous-cell carcinoma*, supposed to develop from remnants of the thyroglossal duct or the branchial clefts (Fig. 342).

Carcinomata of the thyroid are extremely malignant since they compromise the surrounding tissues at an early period of their growth and, therefore, soon become inoperable. They are very apt to metastasize in the bones,[2] particularly of the head and face, the daughter tumors being sometimes so vascular as to pulsate like an aneurysm.

[1] *Honsell*, Beitr. z. klin. Chir. (Bruns), 1899, xxiv, 112 (bibl.). But see *Kanoky*, Surg., Gynec., and Obst., 1916, xxii, 679.

[2] *von Eiselsberg*, Arch. f. klin. Chir, 1893, xlvi, 430; *Middledorpf*, ibid., 1894, xlviii, 502.

Sarcomata[1] of all varieties occur, but offer no peculiarities characteristic of this site,[2] except that the very vascular types, usually designated *hemangiomata* or *endotheliomata*, occur in this organ more frequently than elsewhere.[3]

The less common new growths of the thyroid include the **fibroma, osteoma, carcinosarcoma,**[4] **melanosarcoma,**[5] and **teratoid** tumors containing muscle, bone, cartilage, brain,[6] etc.

It has already been said (page 383) that the cells of a malignant tumor might be temporarily of use to the body by continuing to furnish the material characteristic of the gland which they involve, and an excellent illustration of this is to be found in the thyroid.[7] Indeed, even hyperthyroidism has been reported in connection with tumors of this gland.[8]

PARATHYROID GLANDS.

Closely connected with the thyroid, occasionally within, sometimes without its capsule, are four small gland-like bodies, usually two on each side. These are the parathyroids ("epithelial bodies") and are both embryologically and functionally distinct from the thyroid. Accessory glands are occasionally found.[9]

The parathyroids appear to be of great importance in the metabolism of the body, since their complete removal apparently usually leads to fatal tetany. It has been shown by MacCallum and Voegtlin[10] that the calcium salts of the body are rapidly excreted on the removal of the parathyroids in dogs, and that the symptoms of tetany following the removal cease on the administration of calcium salts. It is inferred from these observations that the parathyroids control the calcium metabolism of the body. Collip[11] has succeeded in preparing a very potent extract of the parathyroid which causes active mobilization of calcium and has proved of therapeutic value in tetany.[12] Its administration also mobilizes lead phosphate which is deposited in the bones in lead poisoning and its use has been suggested in detoxicating such patients.

TUMORS.

Neoplasms of the parathyroid are so rare that only some thirty cases[13] are to be found in the literature. The great majority are benign; and

[1] *Marf*, Jour. Am. Med. Assn., 1899, xxxii, 911 (bibl.); *Binnie*, Surg., Gynec., and Obst., 1918, xxvi, 288; vii, 357 (bibl.); *Saltykow*, Centralbl. f. allg. Path., 1905, xvi, 547 (bibl.); *Simmonds*, Ztschr. f. Krebsforsch., 1913, xiii, 307.

[2] For a review of malignant tumors of the thyroid in general, see *Müller* and *Speese*, Univ. Pennsylvania Med. Bull., 1906–07, xix, 74 (bibl.). For the clinical aspect of thyroid tumors, see *Crotti*, Thyroid and Thymus, Philadelphia and New York, 1918.

[3] *Hedinger*, Frankfurt. Ztschr. f. Path., 1909, iii, 487.

[4] *Loeb*, *Leo*, Am. Jour. Med. Sc., 1903, cxxv, 243 (bibl.); *Wells*, Jour. Path. and Bacteriol., 1901, vii, 357 (bibl.); *Saltykow*, Centralbl. f. allg. Path., 1905, xvi, 547 (bibl.); *Simmonds*, Ztschr. f. Krebsforsch., 1913, xiii, 307.

[5] *Franckel*, Prag. med. Wchnschr., 1897, xxii, 321; abstr. in Centralbl. f. allg. Path., 1900, xi, 246.

[6] See, for example, *Flesch* and *Winternitz*, Jahrb. f. Kinderheilk., 1905, lxii, 410; abstr. in Centralbl. f. allg. Path., 1906, xvii, 346.

[7] *von Eiselsberg*, Arch. f. klin. Chir. (Langenbeck), 1894, lxviii, 489; abstr. in Centralbl. f. allg. Path., 1895, vi, 1671.

[8] *Löwy*, Wien. klin. Wchnschr., 1909, xii, 1671.

[9] For a study of the parathyroids, with bibl., see *Thompson*, *R. L.*, Jour. Med. Research, 1906, N. S. x, 399; *MacCallum*, Ergebn. d. inn. Med., 1913, xi, 569 (bibl.).

[10] *MacCallum* and *Voegtlin*, Bull. Johns Hopkins Hosp., 1908, xix, 91, and Jour. Exper. Med., 1909, xi, 118.

[11] *Collip*, *J. B.*, Jour. Am. Med. Assn., 1927, lxxxviii, 565.

[12] *McCann*, Jour. Am. Med. Assn., 1927, lxxxviii, 566.

[13] *Bérard* and *Alamartine*, Lyon chir., 1908–09, i, 721 (bibl.).

such growths are often discovered accidentally at autopsy,[1] though it is frequently impossible to decide whether a given enlargement is an adenoma or merely a hyperplasia.[2]

Tumors of the parathyroids have been found in patients suffering from osteitis deformans and osteitis fibrosa, but no definite causal relationships between the bone conditions and the tumors can be assumed at present.

Malignant growths are extremely rare, only about 10 per cent. of the few recorded cases having been malignant metastasizing neoplasms.[3]

Metastatic growths in the parathyroids are rare.[4] The usual source of such metastases has been carcinomata of the breast, esophagus and thyroid. Metastases from lymphosarcoma have also been noted.

The Adrenals. (Suprarenal Bodies, Suprarenal Capsules.)

Malformations.

In acephalic and other monsters the adrenals may be atrophied or entirely absent. Sometimes in well-formed adults these organs cannot be discovered. There may be little rounded nodules loosely attached to the surface of the adrenals and having the same structure. Accessory and misplaced adrenals are not uncommon. A few cases have been reported of accessory adrenals in the broad ligament.[5] They may be present in the liver.[6]

If one kidney be absent or in an abnormal position its adrenal usually retains its normal position.[7]

The removal of both adrenals in animals causes weakness, convulsions, rapid respiration due to the hypersensitivity of the respiratory center, coma, and death in thirty-six to seventy-two hours. The blood pressure and temperature also fall. Transfusions of adrenalin do not prevent these symptoms. A similar picture is seen in human beings following injury, hemorrhage, hemorrhagic infarction due to emboli and suppurative processes involving both adrenals. Evidence of adrenal insufficiency is seen in many cases of extreme sepsis.

If one adrenal is absent there may be a compensatory hyperplasia of the other, and similar compensatory hyperplasia may occur in unilateral tuberculosis or the destruction of one adrenal by syphilitic lesions. In young animals a similar cortical compensatory hyperplasia can be induced by the excision of one adrenal, but it has not been possible to demonstrate a true hyperplasia of the medullary portion of the gland. Hypertrophy of the adrenal cortex has also been noticed in cases of pseudo-hermaphroditism. Such hypertrophy is accompanied by an atrophy of the ovaries, internal genital organs, and absence of the secondary sexual characteristics. Similar hypertrophy has been noticed after castration of animals. Such hypertrophy is evidently closely connected with the metabolism of lipoids and therefore is correlated with such physiological and pathological conditions as lead to an increase in cholesterol in the blood. The amount of such cortical lipoid is increased in chronic nephritis, arteriosclerosis, diabetes, and cardiac decompensation.

The exact mechanism of the adrenal function is still undetermined, for it has not yet been finally shown whether there is a constant outflow into the blood of a specific secretion to keep up the vasomotor tonus. It is quite probable that an active secretion does take place under an emotional or a nervous stimulus, as evidenced both

[1] *Harbitz*, Jour. Med. Research, 1915, N. S. xxvii, 361 (bibl.). For a discussion of the symptomatology of parathyroid tumors, see *Gussio*, Policlinico, Rome, 1910, xvii, Sezione Chir., 494.

[2] *Da Costa*, Surg., Gynec., and Obst., 1909, viii, 32.

[3] *Bérard* and *Alamartine*, Lyon chir., 1908–09, i, 721; see also *de Quervain*, Deutsch. Ztschr., f. Chir., 1909, c, 334.

[4] *Thompson*, Jour. Med. Research, 1911, N. S. xix, 291.

[5] See *Warthin*, Am. Jour. Obst., 1900, xlii, 797 (bibl.).

[6] See *Noyes, W. B.*, Trans. New York Path. Soc., 1899–1900, p. 4; also *Beer*, Ztschr. f. Heilkunde, Abth. f. path. Anat., 1904, xxv, 381.

[7] For consideration of relationship of the adrenals to the nervous system, see *Alexander*, Zieglers Beitr., 1892, xi, 145 (bibl.).

through the raising of the blood pressure by contraction of the vessels (with the exception of the coronary artery) and through mobilization of the glucose supply in the organs.[1] Nevertheless, the question cannot be settled as yet, as the experimental results are still contradictory.[2]

Another function, probably that of the adrenal cortex which does not produce adrenaline, is shown in the precocious sexual maturity observed in children with tumors of the adrenal cortical tissue; female children may assume some male characteristics.[3] These tumors in adults are sometimes associated with unusual hairiness (*hirsuties*).

ATROPHY AND DEGENERATION.

Atrophy of the adrenals may be extreme.

Fat Infiltration.—An accumulation of fat or of lipoid droplets[4] in the cortical portion is the rule in the adult. It sometimes occurs in

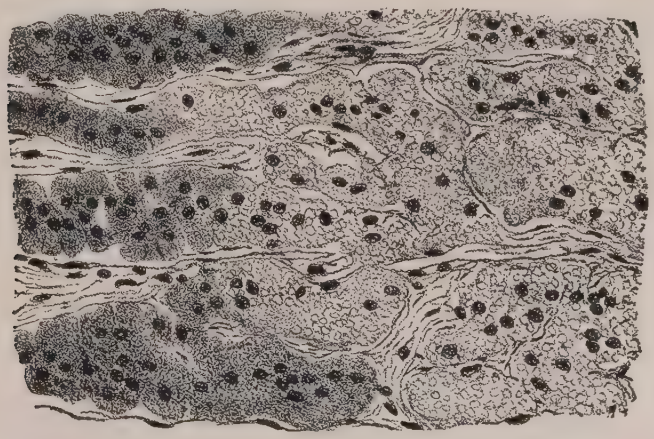


Fig. 343.—Fatty Infiltration of the Adrenal.

nodular areas (Fig. 343). In children under five years of age it is pathological.

Amyloid degeneration may involve both the cortical and medullary portions. In the cortex it usually involves only the walls of the blood-vessels; in the medulla both the blood-vessels and the cells of the parenchyma may undergo this degeneration. The organs are usually firm and have a grayish, semitranslucent appearance.

Pigmentation of the inner cortical zone is frequent in old persons. Focal necroses may occur in infections.

[1] *Cannon*, Bodily Changes in Pain, Hunger, Fear and Rage, New York, 1915.

[2] For views opposed to those of Cannon, see *Stewart, G. N.*, and *Rogoff, J. M.*, Am. Jour. Physiol., 1917, xliv, 543.

[3] *Glynn, E. E.*, Quart. Jour. Med., 1912, v, 157; *Jump, H. D.*, *Beates, H.*, and *Babcock, W. W.*, Am. Jour. Med. Sc., 1914, cxlvii, 568; *Bland-Sutton*, Tumors Innocent and Malignant, New York, 1917, p. 106.

[4] For a study of lipoid substances in the adrenal, see *Herrmann*, Arb. a. d. path. Inst., Tübingen, 1906, v, 417.

THROMBOSIS AND HEMORRHAGE.

Venous and capillary thrombosis may occur.

In children, soon after birth, it is not very infrequent to find large hemorrhages in one of the adrenals, converting it into a cyst filled with blood (Fig. 344). This lesion has been observed in a few cases in adults.[1]

INFLAMMATION.

Suppurative inflammation, with the formation of abscesses, has been seen in a few cases.

The most frequent lesion of the adrenals is **tuberculous inflammation.** They are usually increased in size; their surfaces are smooth or nodular.

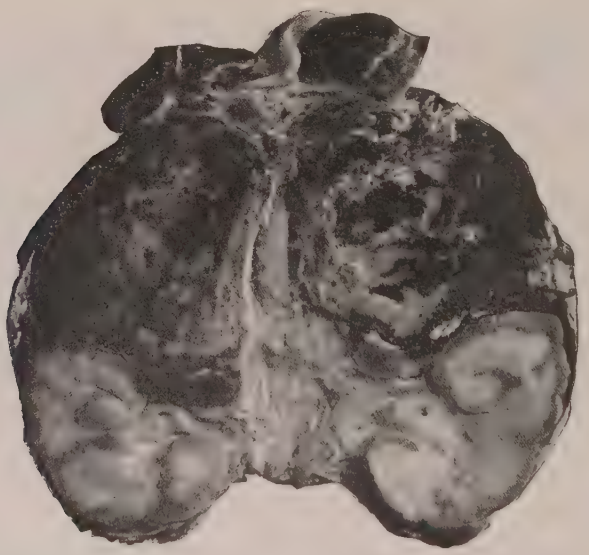


FIG. 344.—HEMORRHAGE INTO AND ABOUT THE ADRENAL. (Infant.)

The normal structure of the gland is more or less replaced by tubercle tissue, which usually undergoes cheesy degeneration and may soften or, in rare instances, calcify and as a final result lead to bone and marrow formation.[2] Fibrous tissue may form in considerable amount. (For a consideration of the relationship of lesions of the adrenals to Addison's disease see page 486.)[3]

Syphilitic inflammation, with and without the development of gummata, is of occasional occurrence.

[1] For bibl., see *Arnaud*, Arch. gén. de méd., 1900, iv, 5.

[2] *Woolley, P. G.*, Jour. Lab. and Clin. Med., 1916, i, 502.

[3] For reference to nature of adrenal secretion, etc., see *Abel*, Vaughan Anniversary Contributions, 1903, 139 (bibl.). For a study of pathology of adrenals, see *Karakascheff*, Zieglers Beitr., 1906, xxxix, 373 (bibl.); see also *Davis*, New York Med. Jour., 1906, lxxxiv, 263 (bibl.).

TUMORS.[1]

Misplaced remnants of the suprarenal body occur in the kidney, testis, ovary, uterus, broad ligament, pancreas, and liver, and about the internal spermatic vein, so that neoplasms composed of adrenal tissue may develop at any of these sites as well as in the gland itself. The most common situation, however, is the kidney (page 908).

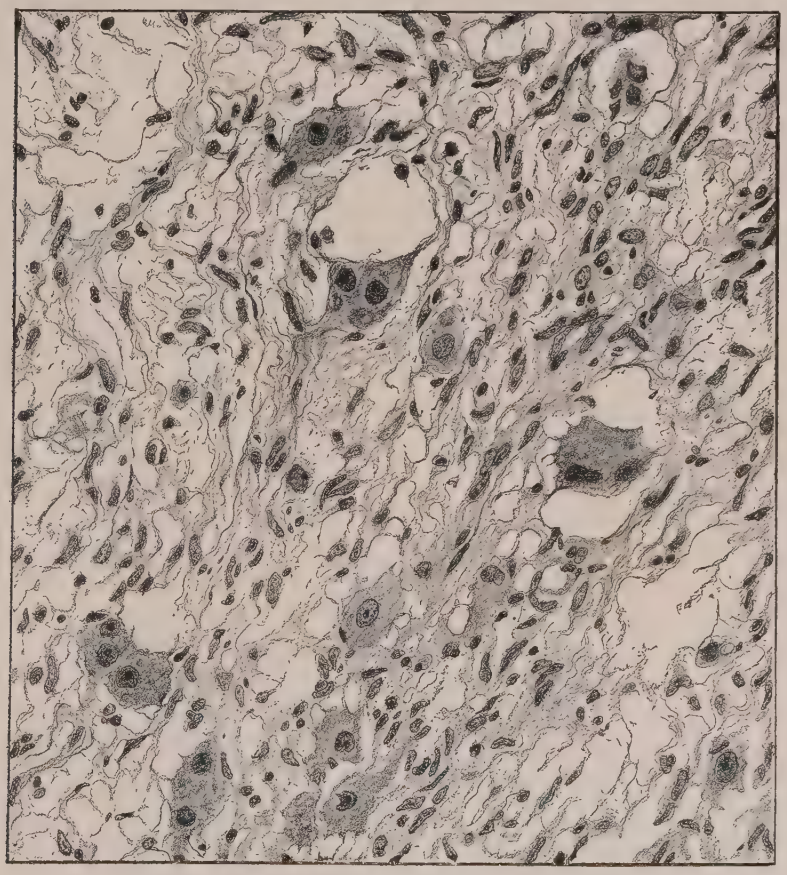


FIG. 345.—CONGENITAL NEUROBLASTOMA OF KIDNEY REGION.

Adenoma (*hyperplasia, hypernephroma, struma suprarenalis*).—This is a rather small growth composed of cortical elements and generally encapsulated or at least well delimited. Diffuse lesions occur, however, and in such an event the question which term to employ—adenoma or hyperplasia—must be a perplexing one. In all these the architectural

[1] For a general discussion of adrenal tumors, see *Woolley, P. G.*, Am. Jour. Med. Sc., 1903, cxxv, 33 (bibl.); *Winkler*, Die Gewächse der Nebennieren, Jena, 1909 (bibl.); of medullary growths, see *Herxheimer*, Zieglers Beitr., 1914, vii, 112 (bibl.). For a review of tumors of the adrenal in lower animals, see *Steinke*, Frankfurt. Ztschr. f. Path., 1910, v, 167. For hypernephroma of the adrenal in a frog, see *Carl*, Centralbl. f. allg. Path., 1913, xxiv, 436.

plan of the normal cortex is followed more or less closely, and the so-called fat droplets in the cells of these growths are largely lipoid as in the normal suprarenal gland. These tumors are occasionally bilateral[1] and may be pigmented.[2]

All grades are found between these small benign growths, which are often discovered accidentally at autopsy, and large necrotic infiltrating and metastasizing neoplasms. The arrangement and morphology of the cells in these malignant tumors approaches much less closely the normal type and whether they should be called adenomata, as they frequently are, is a question. They have been termed *malignant hypernephromata*, but in the interests of consistency the name hypernephroma might well be abandoned, since in modern terminology appellations are chosen, not according to the organ in which the neoplasm arises, but to the variety of tissue from which it develops. *Carcinoma* and *epithelioma* have also been employed,[3] though as the cortex is derived, not from epithelium, but from mesothelium, it would seem more appropriate to call these growths *mesotheliomata*.[4] The problem, however, is a difficult one and even the best authorities so far have been unable to solve it.

Metastatic carcinomata sometimes involve the adrenal,[5] and even when both glands are destroyed symptoms of adrenal insufficiency may not develop, further proof that a tumor is not always useless to the organism (pages 383 and 595).

Sarcoma.—Many of the growths that have been described as sarcomata are now known to have been neuroblastomata (Fig. 345) or allied tumors (page 418). Some of the others are asserted[6] to belong rather to the "malignant hypernephromata," neoplasms which completely resemble neither the sarcoma nor the carcinoma, but have some of the characteristics of both. The remainder[7] includes *spindle-cell sarcoma*, *myxosarcoma*, and *melanosarcoma* (*melanoma*).[8]

For **glioma** of the adrenal see page 418.

The Carotid Gland.

This is a small, ductless, encapsulated structure, 5 to 7 millimeters long, lying at the bifurcation of the carotid artery and composed of a connective-tissue framework inclosing masses of polyhedral cells grouped about blood capillaries. Some of its cells may stain brown with chromic acid and yield a substance exerting the physiological action of adrenaline.[9] The gland contains many nerves and is believed to represent a paraganglion and to be analogous with the adrenals, the hypophysis cerebri, and

[1] *Prym*, Frankfurt. Ztschr. f. Path., 1913, xiv, 409.
[2] *Lucksch*, Zieglers Beitr., 1912, liii, 324.
[3] *Winckler*, Die Gewächse der Nebennieren, Jena, 1909.
[4] *Woolley* and *Adami*, Tr. Assn. Am. Phys., 1902, xvii, 627 (bibl.). For a discussion of the controversy, see *Davis*, Arch. Int. Med., 1911, viii, 60 (bibl.).
[5] *Reiche*, Centralbl. f. Allg. Path., 1893, iv, 1; *Beitzke*, Deutsch. med. Wchnschr., 1904, xxx, 897.
[6] *Kaufmann*, Lehrbuch d. spezielle pathologische Anatomie, Berlin, 1911, ii, 802.
[7] For a description of sarcoma and other malignant growths of the adrenal, see *Ramsey*, Bull. Johns Hopkins Hosp., 1899, x, 20.
[8] *Schmidt*. Frankfurt. Ztschr. f. Path., 1912, ix, 400.
[9] *Monckeberg, I. G.*, Zieglers Beitr., 1905, xxxviii, 1.

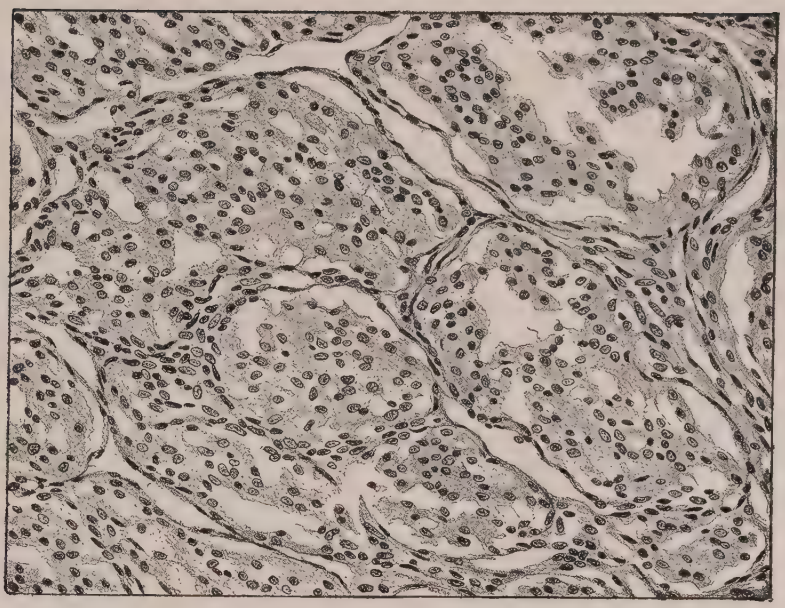


Fig. 346.—Paraganglioma of Carotid—Alveolar Form.

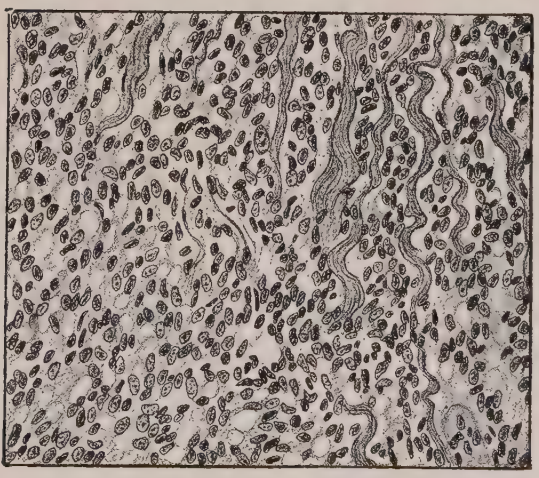


Fig. 347.—Paraganglioma of Carotid—Diffuse Form.

the coccygeal gland. Total extirpation of the carotid gland causes glycosuria in animals.[1]

Tumors.

Tumors of the carotid gland are very infrequent. In their structure they more or less closely imitate the morphology of the normal organ; usually they possess an alveolar structure, the alveoli being bordered by delicate capillaries (Fig. 346). Occasionally, there is no definite arrangement, and the tumors appear more like a carcinoma (Fig. 347). Chromaffin cells have been demonstrated in some of the tumors of this gland.[2]

[1] *Massaglia*, Frankfurt. Ztschr. f. Path., 1916, xviiii, 333.

[2] For further details and bibl. of tumors of the carotid, see Paraganglioma, p. 423.

CHAPTER V.

THE CIRCULATORY SYSTEM.

The Pericardium.

INJURIES.

The pericardium may be injured by penetrating weapons, by gunshot wounds, and by the cutting action of sharp fragments of bone. It may be ruptured by severe contusions of the thorax, and by rapid extravasation of blood into the pericardial sac. Perforations may occur with empyema, mediastinal abscesses, and abscesses of the chest wall and of the liver, or in connection with aneurysms of the aorta and suppurative inflammation of the pericardium.

HEMORRHAGE. (Hemopericardium.)

Extravasations of blood into the cavity of the pericardium may follow wounds and rupture of the heart, rupture of the aorta and of aneurysms, and may occur with pericarditis from the rupture of new-formed blood-vessels. Small extravasations in the substance of the pericardium are found with scurvy, purpura, leukemia, anemia, and poisoning with phosphorus or benzol, after very severe dyspnea, and in infectious diseases.

HYDROPERICARDIUM. (Dropsy.)

At autopsies performed a few hours after death, a few cubic centimeters of clear, light-yellow serum are usually found in the pericardial sac. If decomposition have commenced, this may be reddish, or it may be slightly turbid from the falling-off of the pericardial endothelium. The presence of considerable amounts of fibrin indicates an inflammatory origin of the fluid.

Large accumulations of clear yellowish serum are often present as part of general dropsy from heart disease, kidney disease, etc. The amount is sometimes so great as to interfere with the movement and nutrition of the heart.

PNEUMOPERICARDIUM.

Air or gas in the pericardium may be the result of post-mortem decomposition and there may then be drying of portions of the pericardium. Wounds or paracentesis of the pericardium; the perforation of carcinomata or ulcers of the stomach, cavities of the lungs, and ulcers of the esophagus, or subdiaphragmatic abscess, may admit air into the

pericardial cavity.[1] In purulent pericarditis with foul, decomposing exudate, gases may be evolved.

INFLAMMATION. (Pericarditis.)

Pericarditis is rarely primary, but is usually secondary to infectious diseases, such as pneumonia, pleurisy, tuberculosis, typhoid fever, endocarditis, and pyemia. It may follow injuries and is frequently associated with rheumatism or inflammation of the kidneys. It may be *exudative* or *productive* in character.

Exudative Pericarditis.—It is convenient to distinguish in exudative pericarditis a *fibrinous*, a *serofibrinous*, and a *purulent* form.

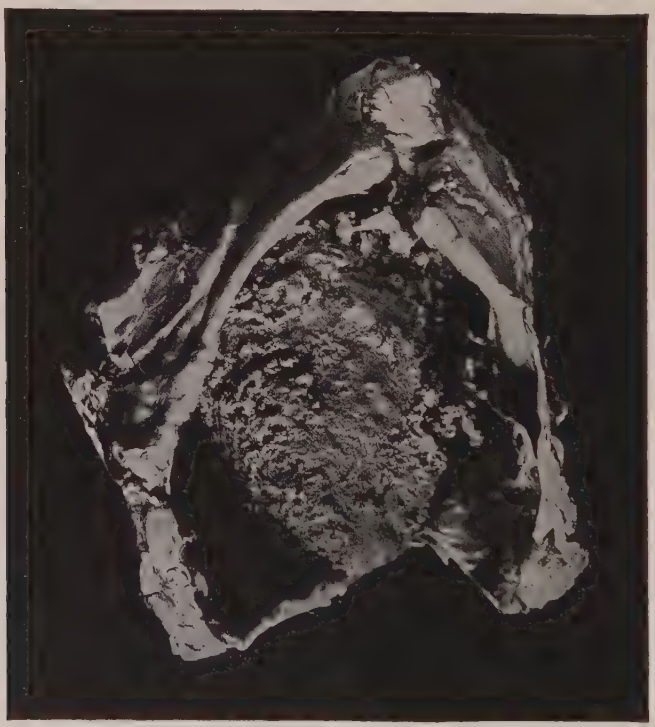


Fig. 348.—Fibrinous Pericarditis.
The pericardial sac is laid open and the heart is seen covered with an irregular villous layer of fibrin.

Fibrinous and Serofibrinous Pericarditis.—In the earlier stages or lighter forms of fibrinous pericarditis, the whole surface or portions of the pericardium may be dull or slightly roughened from a delicate fibrinous pellicle, more or less hyperemic, and often studded with minute petechiæ. Later, if the exudate accumulate, the entire surface of the pericardium may be covered with a net-like layer of thick masses of fibrin. This may cover both the visceral and parietal surfaces and

[1] See *James*, Am. Med., 1904, viii, 23.

is often beset with irregular villosities (Fig. 348). Fibrinous adhesions may form between the two layers. There is usually some serous fluid as well as leucocytes mingled with the fibrin.

Serum may accumulate in considerable quantity—*serofibrinous pericarditis*. The pericardial sac may be greatly distended with this form of exudate so as to displace the heart and compress the larger air passages, the esophagus, or the aorta.

Purulent Pericarditis.—In this form of exudative pericarditis there are usually more or less serum and fibrin mingled with pus cells and often red blood-cells. The process may start as a serofibrinous inflammation. It is apt to occur as an extension of an infectious process in the neighborhood or as a part of a general pyemic process. Streptococcus pyogenes, Diplococcus pneumoniæ, Staphylococcus pyogenes aureus, and the tubercle bacillus are the bacteria most commonly found in exudative pericarditis.

Fig. 349.—Adhesions of the Pericardium.

The pericardial sac is opened so that the heart is viewed from the direction of the apex. There are two clusters of delicate fibrous bands joining the parietal and the visceral pericardium.

Chronic Pericarditis.—In exudative pericarditis the mesothelium[1] (endothelium) in the early stages, and later this with the underlying connective tissue cells contributes to the cellular elements in the exudate. In recovery the exudates degenerate and are gradually absorbed, while from the blood-vessels and the connective-tissue cells of the pericardium more or less new fibrous tissue is formed, at first very cellular and vascular, later dense in character. There may, finally, be local or general thickenings of the pericardium. If a moderate amount of new fibrous tissue is formed this may appear as thin, white patches on the surface of the pericardium, the so-called *maculæ tendineæ*. The new fibrous tissue may

[1] *Minot, C. S.*, Science, 1901, xiii, 481.

extend between the subpericardial muscle fibers of the heart; and calcification of this new-formed fibrous tissue may occur. More or less permanent adhesions may form between the visceral and parietal pericardium; and these may be in the form of delicate fibrous strings (Fig. 349) or of larger areas of firm adhesion.[1]

Obliteration of the Pericardial Sac.—As the result of the formation of vascular new connective tissue between the pericardial walls, the sac may be partially or wholly obliterated (Fig. 350).

This may be the conclusion of an acute inflammatory process or it may result from the organization of a blood-clot following hemorrhage into the sac. It may occur as the result of the latter process early in life.

Supra-arterial Epicardial Fibroid Nodules.—Small fibrous nodules are occasionally formed along the branches of the coronary arteries, especially on the surface of the ventricles. They are frequently

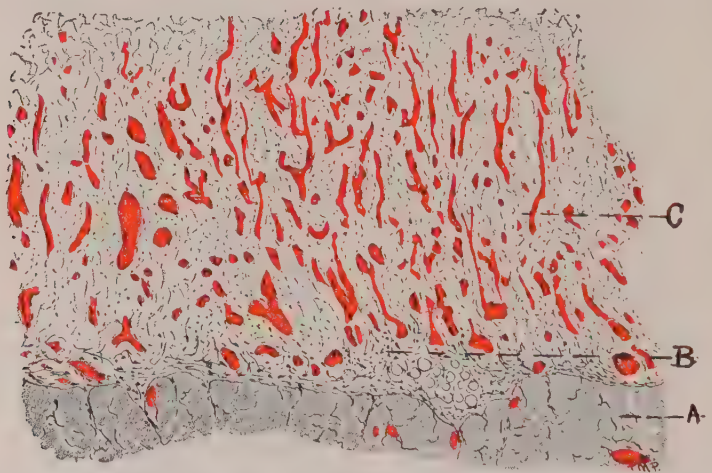


Fig. 350.—Obliteration of the Pericardial Sac in a Child, Following Pericarditis.

Showing blood-vessels growing from the visceral pericardium into the blood-clot filling the sac. Transverse section. *A*, Heart; *B*, pericardium; *C*, new-formed vascular tissue extending above to the unorganized clot. A similar layer of new vascular tissue was present over the parietal pericardium, and in places the two layers had coalesced, obliterating the sac.

associated with lesions of the arteries,[2] leading to the weakening of their walls at these situations, but are not to be confused with the lesion called *periarteritis nodosa* (page 654), though they closely resemble it grossly.

Tuberculous Pericarditis.—This lesion may occur by itself, but is apt to be associated with other tuberculous inflammation in the vicinity of the heart. There may be miliary tubercles scattered diffusely, or limited to certain regions in the pericardium, which is otherwise little changed. Not infrequently, however, there is a considerable thickening of the pericardium, either visceral or parietal, or both.

In such cases the new-formed tissue consists of fibrous tissue and of

[1] For a study of such cases, see *Smith, W. H.*, Jour. Am. Med. Assn., 1913, lxi, 739.
[2] *Knox, M.*, Jour. Exper. Med., 1899, iv, 245.

tubercle tissue which has undergone extensive cheesy degeneration (Fig. 351). The thickened visceral and parietal layers of the pericardium are often more or less grown together, so that the pericardial sac may be partially or almost completely obliterated. An inflammatory exudate often accompanies the tuberculous process.[1]

TUMORS.

Tumors of the pericardium are rare, though **fibroma,**[2] **lipoma,**[3] **hemangioma,**[4] and **sarcoma**[5] have been described. Free masses of fat have been found in the pericardial sac.

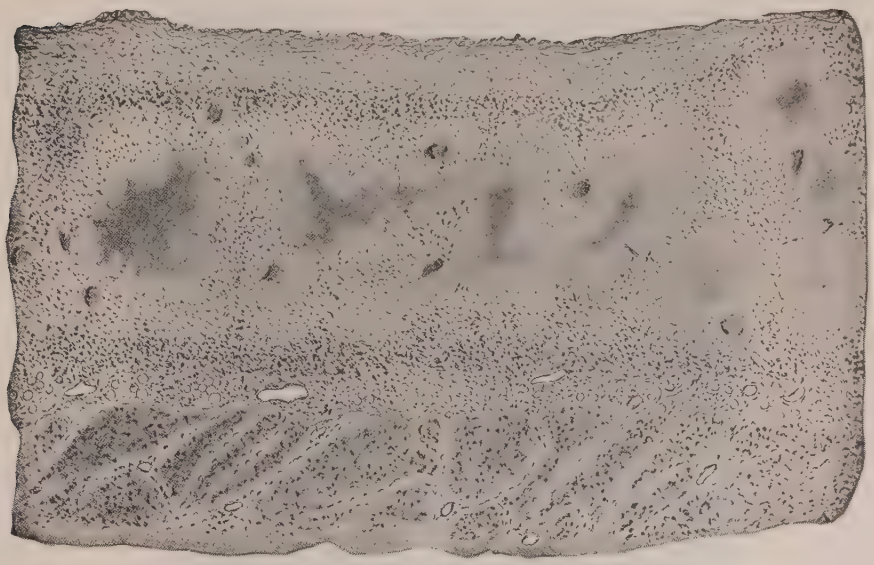


FIG. 351.—TUBERCULOUS PERICARDITIS.
The greatly thickened pericardium shows diffuse tissue with giant cells and irregular areas of cheesy degeneration. The free—upper—surface is covered with a layer of fresh fibrin.

Cysts of the visceral pericardium have been described. Prudden has seen a pedunculated cyst, containing about 6 c.c. of clear fluid, hanging into the pericardial sac from its attachment near the pulmonary artery. Similar edematous polyps are described by Kaufmann.[6] The origin of such cystic masses is obscure, but they may be derived from the growth of the pericardial mesothelium over deposited masses of fibrin, which then soften and thus form a pedunculated cyst. Small blebs of fluid along such mesothelial overgrowths are not uncommon in chronic pericarditis.

[1] For bibl. of tuberculous pericarditis, see *Norris*, Univ. Pennsylvania Med. Bull., 1904, xvii, 155.
[2] *Forni*, Tumori, 1914–15, iv, 522 (bibl.).
[3] *Struppler*, München. med. Wchnschr., 1907, liv, 472.
[4] *Timme*, Cleveland Med. Jour., 1915, xiv, 453.
[5] *Tobiesen*, Ztschr. f. klin. Med., 1912, lxxv, 53 (bibl.).
[6] *Kaufmann*, Lehrbuch d. spez. path. Anatomie, 3d ed., Berlin, 1911, i, 12.

The Heart.

Malformations and Malpositions.[1]

Malformations of the Heart.—The malformations of the heart are usually closely associated with malformations of the aorta and pulmonary artery. They depend on arrest of, or abnormal, development; on endocarditis, myocarditis, thrombosis, or mechanical causes.

I. The common arterial trunk is only partially, or not at all, separated into aorta and pulmonary artery. The divisions between the heart cavities are at the same time defective, so that there may be one ventricle and no auricles; one ventricle and one auricle—reptilian heart (Fig. 352); or one ventricle and two auricles.

II. The trunk of the pulmonary artery or of the aorta is stenosed or obliterated, and from the obstruction to the current of blood there is interference with the development of the septa between the heart cavities.

Fig. 352.—Reptilian Heart.
Shows one auricle and one ventricle.[2]

1. The aorta, at its origin, or in the ascending portion of the arch, is stenosed or closed. The pulmonary artery gives off the descending aorta, and supplies the carotids and subclavians. The foramen ovale remains open, or there is no septum between the auricles. The ventricular septum is also usually defective. The right ventricle is hypertrophied.

2. The pulmonary artery is stenosed or closed (Fig. 353). Its branches are sup-

[1] A just understanding of the malformations of the heart can be obtained only by a study of the normal embryonic development. Good texts are *Bryce, T. H.*, Quain's Anatomy, London, 1908, i, 206; *Keith*, Human Embryology, 3d ed., London, 1913, p. 294; *Broman*, Normale und abnorme Entwicklung des Menschen, Wiesbaden, 1911, p. 519; and *Herxheimer*, Schwalbe, Die Morphologie der Missbildungen des Menschen, Jena, 1910, iii, 339; see, also *Mall, F. F.*, Am. Jour. Anat., 1912, xiii, 249.

[2] For a description of this case, see *Northrup, W. P.*, Trans. N. Y. Path. Soc., 1888, p. 40.

plied by the aorta, through the ductus arteriosus. The ventricular septum is defective, the foramen ovale is open, or the auricular septum defective.

III. The malformation affects the aorta and pulmonary artery after they are more fully developed.

1. There is stenosis of the aorta between the left subclavian and ductus arteriosus, or just at the opening of the ductus arteriosus. The descending aorta is then a continuation of the pulmonary artery.

2. The aorta gives off all its branches from the arch, but the descending aorta is a continuation of the pulmonary artery; or the carotids may spring from the aorta, the subclavians from the pulmonary artery.

FIG. 353.—STENOSIS OF THE PULMONARY ARTERY.
The ductus arteriosus is open.

3. The vessels are transposed; the pulmonary artery arises from the left, the aorta from the right ventricle; the pulmonary veins empty into the left, the venæ cavæ into the right auricle; or the veins also may be transposed. The septa are defective.

IV. The aorta and pulmonary artery are normal, but the cardiac septa are defective.

1. The foramen ovale remains partly open. This condition may continue through life without ill effects. It has been found by some observers in about one-fifth of their autopsies.

2. The ductus arteriosus remains open for many years; this also may cause no disturbance.

3. There is a small or large opening in the ventricular septum, usually in its upper part (Fig. 354). This may give rise to no symptoms, unless disease of the heart or lungs be superadded.

V. Either of the auriculoventricular orifices is entirely closed. The foramen ovale remains open, and the ventricular septum is defective.[1]

VI. The valves of the different orifices of the heart are absent or defective. The arteries or the ventricles are usually defective at the same time.

The aortic and pulmonary valves consist of two large or four small leaves, instead of the usual three.

The edges of the semilunar valves are fenestrated. This alteration is usually of no significance. It is frequent in the aortic and pulmonary valves. The valves may be thinner than normal, and near their free edges are small slits or openings (see Fig. 355).

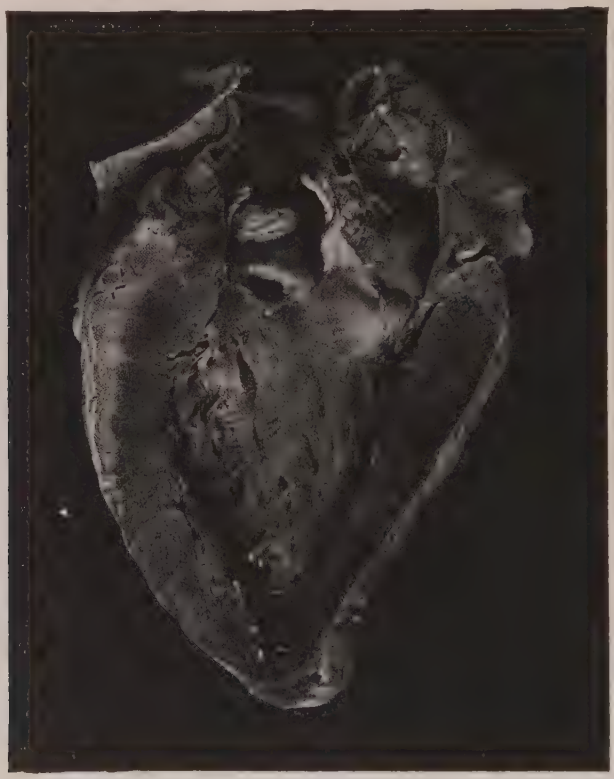


Fig. 354.—Opening in the Ventricular Septum of the Heart—Interventricular Foramen. The opening is about 5 mm. in diameter, and its edges are formed by fibrous tissue.

Generally speaking, the existence of openings between the two auricles or the two ventricles, admitting some admixture of venous and arterial blood, produces no marked change in the circulation. If, however, the passage of the current of venous blood into the right heart is in any way interfered with, the consequences are very serious. Cyanosis is produced, the skin is of a bluish color, the small veins and capillaries are dilated, exudation of serum and hypertrophy of connective tissue take place, especially in the fingers and toes.

There may be absence of the heart; abnormal septa and chordæ tendineæ[2] (Fig.

[1] Consult for a study of rare forms of cardiac anomalies, *Hektoen*, Am. Jour. Med. Sc., 1901, cxxi, 163 (bibl.).

[2] For a study of the origin of abnormal chordæ tendineæ in the heart, see *Tawara*, Zieglers Beitr., 1906, xxxix, 563.

356) in the heart cavities; abnormal shapes of the heart. Very rarely two more or less perfect hearts are found in the same thorax.

Malpositions of the Heart.—1. There is a smaller or larger defect in the walls of the thorax, so that the heart projects on the outside of the chest; the pericardium is usually absent.

2. The diaphragm is absent, and the heart is in the abdominal cavity.

3. The heart is in some part of the neck or head; this occurs only in fetuses very much malformed.

4. The heart is transposed, being on the right side, and may be a mirror picture of the normal. This should be distinguished from simple dextrocardia, in which complete reversal of vessels and ventricles does not necessarily occur. The other organs of the thorax and abdomen, also, may be transposed (*situs inversus*) or may not. The former condition is the more frequent.

Abnormal Size of the Heart.—1. The heart may be abnormally large in connection with obstructive anomalies of the great vessels.

2. The heart may be abnormally small (*hypoplasia*). This abnormality is apt to be associated with status lymphaticus (page 500).

Displacements of the Heart.—Changes in the position of the heart are congenital or acquired. The congenital malpositions have already been mentioned.

The acquired malpositions may be associated with:

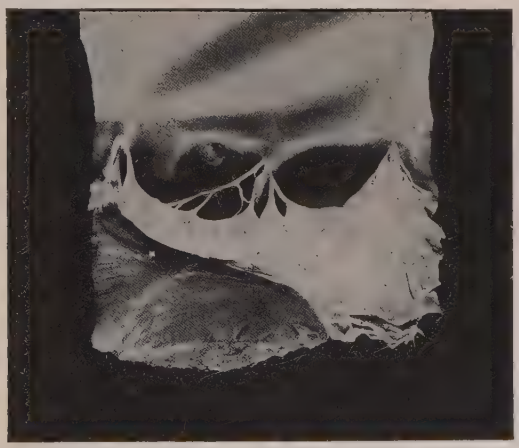


Fig. 355.—Fenestration of the Semilunar Valves.

1. Hypertrophy of the heart; its long axis approaching the horizontal position.

2. Changes in the thoracic viscera. Emphysema of both lungs may push the heart downward. Emphysema, pleurisy with effusion, or pneumothorax of one side pushes the heart to the other side. Pleurisy or chronic pneumonia, producing retraction of one side of the thorax, draws the heart to that side. New growths, aneurysms, and curvatures of the spine displace the heart in various directions.

3. Changes in the abdomen. Accumulations of fluid and new growths in the abdomen, and tympanites, may push the heart upward.

WOUNDS AND RUPTURES.

Wounds of the heart are most frequently made by penetrating instruments, by bullets, and by fragments of bone. The right ventricle is the most frequently wounded (Fig. 357); next the left; rarely the auricles. The wound may penetrate into the cavities of the heart or pass only partly

through its wall, or a bullet or the broken end of a weapon may be embedded in the wall. If the wound penetrates a cavity and is gaping, death may follow instantly and the pericardium be found filled with blood. If the wound is small and oblique, the blood may escape gradually and death may not ensue for several days. In rare cases adhesions are formed with the pericardium and the wound cicatrizes. Wounds which do not penetrate may cause death by the inflammation which they excite, or they may cicatrize. Bullets and foreign bodies may become encapsulated in the heart wall and remain so for years.[1]

FIG. 356.—ABNORMAL CHORDÆ TENDINEÆ.
These unite to form a slender band stretching across the cavity of the ventricle.

Rupture of the heart wall occurs in various ways:

1. Severe contusions of the thorax may produce rupture, usually of one of the auricles.[2]

2. Spontaneous rupture occurs most often in advanced life. Rupture is most frequent in the left ventricle, and, in a considerable proportion of cases, near the apex. There is usually one rupture, but sometimes there

[1] For a study of foreign bodies in the heart, see *Bailey, C. H.*, Arch. Int. Med., 1913, xi, 440.
[2] For bibliography, see *Newton*, Med. Record, 1899, lv, 864. Also *Hamilton, A. S.*, Philadelphia Med. Jour., 1903, xl, 173.

are more. The rupture is usually oblique and larger internally than externally. The heart wall, near the seat of rupture, may be infiltrated with blood, or blood may infiltrate the subpericardial fat. The heart wall may be of normal thickness, or thin; it is usually soft and in a condition of fatty infiltration or degeneration. The rupture very frequently takes place when the patient is quiet. Death may be almost instantaneous or may not ensue for several hours.

Fatty degeneration leading to rupture of the heart may be general, but it is frequently circumscribed and due to obliterating endarteritis, atheroma, thrombosis, or embolus of one of the coronary arteries, whereby a portion of the heart wall is deprived of nourishment and degenerates. Or

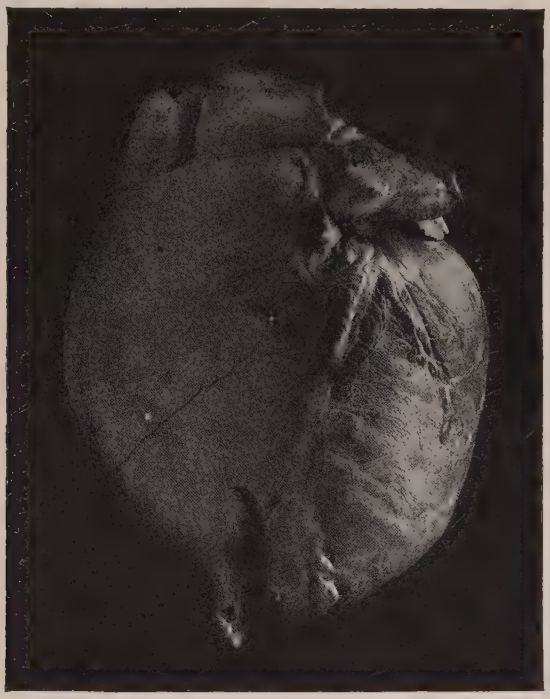


Fig. 357.—Rupture of the Heart.
From contusion.

rupture of a branch of one of the coronary arteries may induce rupture of the heart wall. Acute and chronic myocarditis, with or without the formation of abscess or cardiac aneurysm, or the presence of tumors in the heart wall, or hydatids, may lead to rupture.[1]

3. In rare cases rupture is associated with stenosis of the aorta and dilatation of the heart cavities.

4. Rupture of the papillary muscles and tendons may be due to fatty degeneration or inflammatory or ulcerative processes.

[1] For a study of sudden deaths due to the heart, consult *Councilman, W. T.*, Boston Med. and Surg. Jour., 1893, cxxix, 457.

ATROPHY.

Atrophy of the walls of the heart may be accompanied with no change in the size of its cavities; or with dilatation (passive dilatation); or, more frequently, with diminution in the size of the cavities.

The atrophy involves most frequently all the cavities of the heart, but may be confined to one or more of them.

The muscular tissue appears normal, or may be brown from the presence of little granules of iron-free, lipoid pigment in the muscle fibers—*brown atrophy;* or the muscle fibers may undergo fatty degeneration; or there may be an abnormal accumulation of fat beneath the pericardium; or there may be a peculiar gelatinous material beneath the pericardium—this consists of fat which has undergone mucous degeneration. The heart may be so much atrophied as to weigh only four ounces.

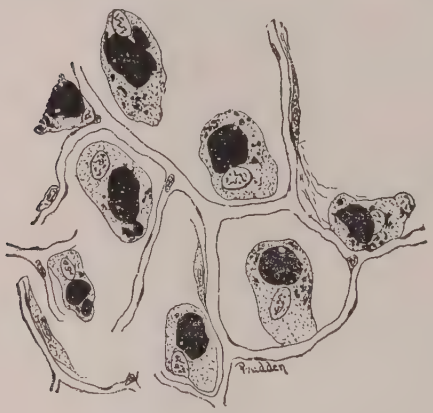


Fig. 358.—Atrophic Pericardial Fat Tissue.

From a young person dead of carcinoma of the stomach and peritoneum. Stained with osmic acid and teased.

Atrophy of the heart may be congenital; it may be associated with repeated hemorrhages, with wasting diseases or senility, with chronic pericarditis, with effusion, with obstructive lesions of the coronary arteries, with chronic myocarditis, or with mitral stenosis.

Atrophy of the pericardial fat tissue not infrequently occurs in persons emaciated by chronic disease, and then the usual situations of the fat are occupied by a tissue resembling mucous tissue in its gross characters. Microscopical examination shows that in this atrophic fat the fat cells have largely lost their contents, and the whole tissue has undergone a partial reversion to its embryonic form (Fig. 358).

ANEURYSM OF THE HEART AND VALVES.

Aneurysm of the Heart.—Sacs filled with blood, situated in the walls of the heart and communicating with its cavities, are formed in several different ways:

1. In interstitial myocarditis a small or large portion of the wall may be replaced by fibrous tissue, and this, yielding to the pressure of the blood from within, may be pressed outward. Such a pouch may be a circumscribed sac communicating with the heart cavity by a small opening, or may be a simple dilatation of part of the ventricle. The wall of such an aneurysm becomes thinner as the sac increases in size. It is composed of the endocardium, new fibrous tissue, visceral pericardium, and

sometimes the adherent parietal pericardium. The walls may calcify, or rarely may become so thin as to rupture externally or into the right ventricle. The sacs may contain fluid blood or be filled with fibrin.

Such aneurysms are usually situated in the wall of the left ventricle; rarely in that of the left auricle. If they are in the septum they may project into the right ventricle or auricle (Fig. 359). They are usually single, but sometimes two or three are found in the same heart.

2. Fatty degeneration of the heart wall may reach such a degree that the wall yields and is pouched out into an aneurysmal sac.

Fig. 359.—Aneurysm of the Heart Opening from the Left Ventricle into the Right Auricle Seen from behind.

3. Endocarditis and myocarditis, or fatty degeneration, may so soften a portion of the heart wall that the endocardium and part of the muscular tissue are ruptured and a ragged cavity is formed. This form of aneurysm usually does not attain a large size, but soon ruptures externally and causes the death of the patient.

Small aneurysms of the sinus of Valsalva are of occasional occurrence.

Aneurysms of the Valves.—These are formed in two ways:

1. They are the result of endocarditis. One of the lamellæ of the leaf of a valve is destroyed, and the other lamella is converted into a sac

filled with blood. These aneurysms are found in the aortic valve, projecting into the ventricle, and in the mitral valve, projecting into the auricle. Not infrequently the wall of the aneurysm gives way, so that there is a rupture entirely through the valve.

2. The entire thickness of a leaf of a valve is pouched, forming a sac filled with blood. This occurs in the aortic, mitral, and tricuspid valves.

THROMBOSIS OF THE HEART.

It is common to find in the heart cavities, after death, yellow, succulent, semitranslucent masses. They are most common and of firmest texture in persons who die of acute inflammatory diseases. They may

FIG. 360.—POLYPOID THROMBUS IN THE LEFT AURICLE OF THE HEART.
The thrombus was dark red in color, with smooth surface.

adhere quite firmly to the walls of the heart and may extend in long, branching cords into the vessels. They are formed in the last hours of life and just after death, and are not of clinical or pathological importance. It is, however, often difficult to determine to what extent such masses have been formed during life, for the so-called "agonal" clots may be continuous with those formed some time before death as well as with those formed after life has become extinct.

Coagula of the fibrin of the blood in the heart form during life, and may exist for years. If the fibrin adheres to the valves in small masses these are called vegetations; if it coagulates in the heart cavities in larger bodies they are called thrombi or heart polypi.

Such thrombi are found in any of the heart cavities. They form

flattened masses firmly adherent to the endocardium; or rounded bodies in the spaces between the trabeculæ; or have a polypoid shape and are attached by a narrow pedicle (Fig. 360 and 361); or very rarely are globular and free in the cavity of the auricle (Fig. 362). Cardiac thrombi are most frequent in the auricular appendages and between the columnæ carneæ near the apices of the ventricles (Fig. 363).

They are usually found in connection with some valvular lesion (Fig. 364), which involves a roughening of the surface, or prevents the free circulation of blood through the heart.[1]

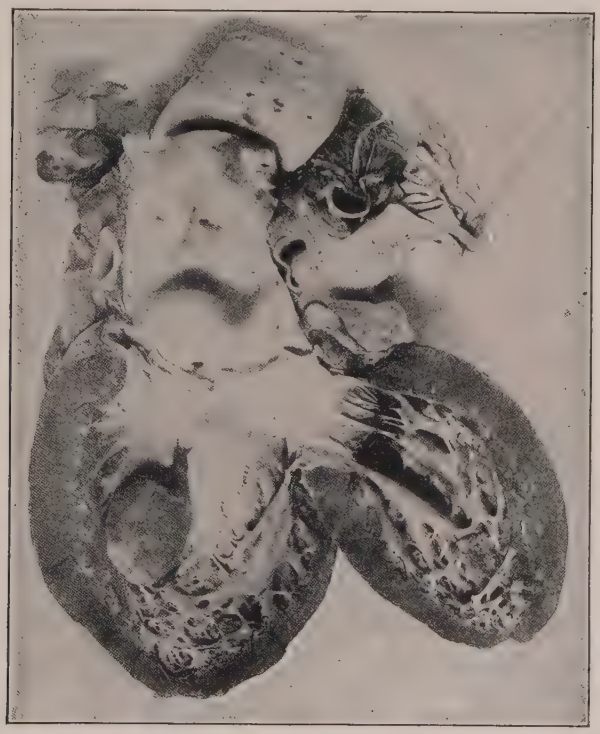


Fig. 361.—Globular Thrombus in the Left Ventricle.
This thrombus was softened at its center.

Old cardiac thrombi are firm, dry, and of a whitish color; they may soften and break down at their centers, so as to look like cysts filled with pus; or they may calcify. They are usually entirely unorganized, consisting simply of fibrin, but may become organized.

Cases are reported of organized thrombi in the auricles, the seat of tuberculous inflammation.[2]

Malignant tumors especially hypernephromata may be accompanied

[1] For a study of cardiac thrombosis, see *Martin* and *Rennie*, Lancet, 1899, ii, 782. See also *Welch*, Allbutt, System of Medicine, 1906, vi, 182.

[2] *Kotlar*, Centralbl. f. Bakteriol., Orig. I, 1894, xv., 498; also *Moser*, Boston City Hosp. Rep., 1900, 11th ser., p. 194.

by the formation of thrombi in the heart cavities, which are composed partly of coagulated blood, partly of tumor tissue.[1]

DEGENERATION.

Albuminous Degeneration. (Parenchymatous Degeneration.)—This lesion frequently occurs in diphtheria,[2] typhoid and typhus fever, pyemia,

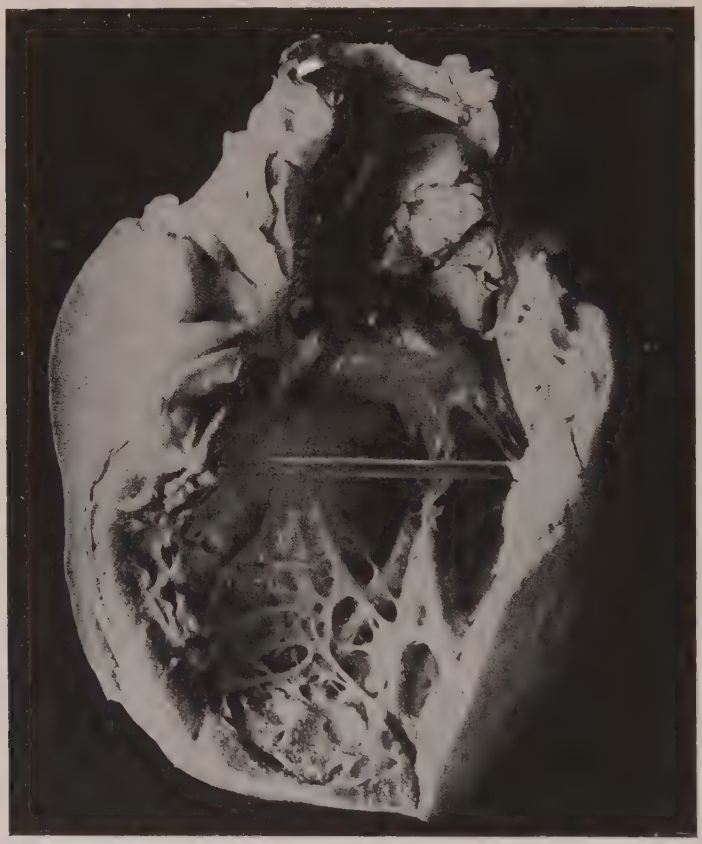


FIG. 362.—LARGE GLOBULAR THROMBUS IN THE RIGHT AURICLE OF THE HEART.

erysipelas, and other infectious diseases, as a result of burns, and under a variety of other conditions. It is characterized by the presence in the muscle fibers of the heart of greater or less numbers of albuminous granules of various sizes, most of them very small. They are not as refractile as fat droplets, and are insoluble in ether, while swelling up and becoming almost invisible under the influence of acetic acid. Sometimes they are so abundant as to conceal the striations of the fibers. The degeneration is usually quite uniformly diffused through the heart, whose

[1] *Kirschner, M.*, Berl. klin. Wchnschr., 1911, ii, 1746, (bibl.).
[2] *Scagliosi, G.*, Virchows Arch., 1896, cxlvi, 115.

walls are softer than normal and of a grayish color. This lesion may be associated with or followed by fatty degeneration.

Fatty Degeneration of the Heart Muscle.—This consists in the appearance in the muscle fibers of the heart of fat or closely allied substances,[1] which collect in larger and smaller droplets, sometimes few in number, sometimes so abundant as almost entirely to replace or conceal the normal striations (Fig. 365). These droplets are soluble in ether,

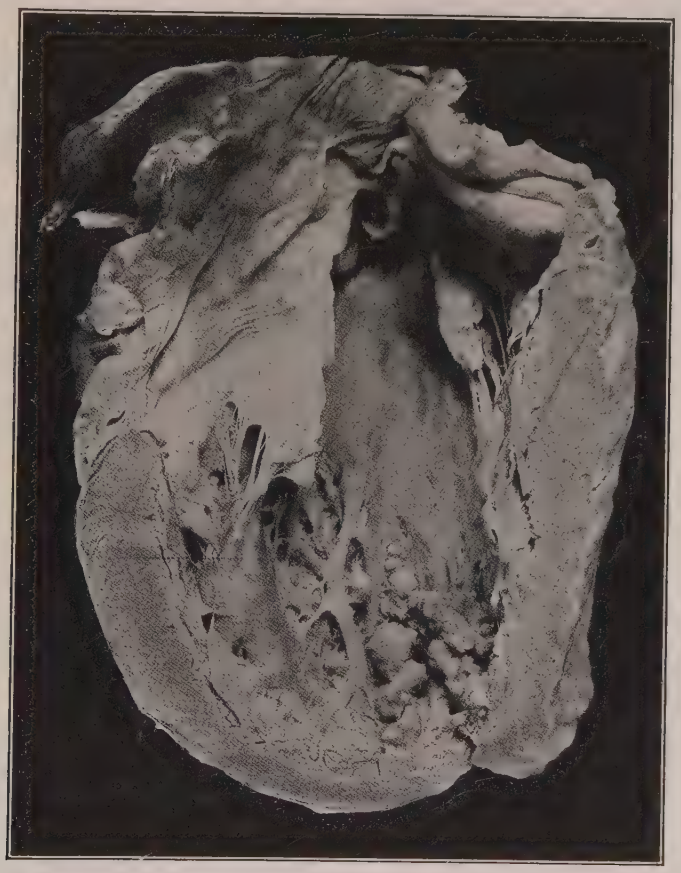


FIG. 363.—THROMBI AMONG THE TRABECULÆ OF THE HEART.

and remain unchanged on treatment with acetic acid. This change is sometimes quite universal, but is more apt to occur in patches, giving the heart muscle a tigroid striation or mottled appearance, which can usually be best seen on the papillary muscles. The degenerated areas have a pale yellowish color, and the muscle tissue is soft and flabby; but when moderate or slight in degree the gross appearance may be little changed, and microscopical examination be necessary for determination of the lesion. This degeneration may lead to thinning of the walls, or

[1] See, in this connection, p. 53.

to rupture of the heart, or to inability to fulfil its functions. It is not infrequently the cause of sudden death.

Fatty degeneration may be secondary to hypertrophy of the heart, to inflammation of the heart muscle, to pericarditis; or to disturbances of the circulation of the coronary arteries by inflammation, atheroma, etc. It may be due to deteriorated conditions of the blood in wasting diseases, excessive hemorrhages, exhausting fevers, leukemia, etc., to poisoning with phosphorus and arsenic, and to the toxins of microbic origin developed in infectious diseases, such as diphtheria, scarlatina, typhoid fever, etc.[1] It may occur in otherwise apparently healthy persons.

Fig. 364.—Thrombus Formed over the Roughened Edge of the Mitral Valve.

Fatty Degeneration of the Endocardium.—It is not uncommon to find, especially in elderly persons, fatty degeneration occurring in patches, especially on the valves, but also on the general endocardium. It may also occur in ill-nourished and anemic individuals. Small, or even considerable, areas of fatty degeneration appear, as a rule, to be of little or no clinical significance; they are at least not inconsistent with perfect health. In these areas of fatty degeneration the connective tissue cells are more or less completely filled with larger and smaller fat droplets. Glycogen is especially abundant in the muscle fibers of the auricles and in those of the conducting system.

Amyloid degeneration of the endocardium or the walls of the blood-vessels and intermuscular connective-tissue septa is a not very infrequent, but usually not very important, lesion. The muscle fibers do not show amyloid changes.[2]

Hyaline degeneration sometimes occurs in the blood-vessels and in the muscle fibers.

There may be **calcification** of the products of inflammation in pericarditis, or of connective-tissue membranes in chronic pericarditis; in the latter case the heart may be more or less inclosed by a calcareous shell. The muscle

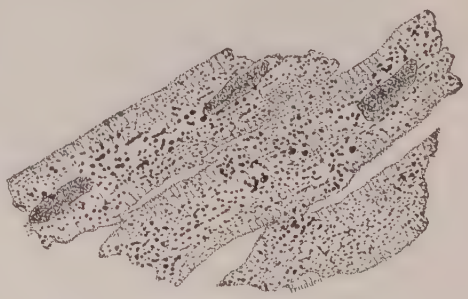


Fig. 365.—Fatty Degeneration of Heart Muscle.

[1] Consult *Flexner*, Bull. Johns Hopkins, 1894, v, 26. For focal fatty degeneration of heart associated with Treponema pallidum, see *Warthin*, Jour. Am. Med. Assn., 1912, lviii, 409.

[2] *Huebschmann, P.*, Virchows Arch., 1907, clxxxvii, 35; *Beneke, R.*, and *Bönning, F.*, Zieglers Beitr., 1908, xliv, 362.

fibers of the heart wall may, though rarely, become densely infiltrated with calcium phosphate. The deposition of the lime salts is generally preceded by degeneration of the muscle. The phenomenon is observed in osteomalacia, in interstitial nephritis, and in areas of degeneration following infections or embolic necrosis.[1]

Fatty Infiltration.—This lesion, which should be clearly distinguished from fatty degeneration, consists of an unusual accumulation of fat about the heart and between its muscle fibers.

The subpericardial fat, which may be present in considerable quantity under normal conditions, may be so greatly increased in amount as to form a thick envelope inclosing nearly the entire organ. Sometimes the accumulation of fat extends into the walls of the heart, between the muscles, causing atrophy of the latter, frequently to a very great extent

FIG. 366.—FATTY INFILTRATION OF THE HEART—LIPOMATOSIS.
The lesion is excessive, the heart muscle being to a large extent atrophied. (The fat cells are represented in the drawing, for the sake of clearness, of relatively too large size.)

(Fig. 366), so that the function of the heart is seriously interfered with. This occurs sometimes in general obesity, or as a result of chronic pericarditis, or in drunkards, or in debilitated or old persons.

SEGMENTATION AND FRAGMENTATION OF THE MYOCARDIUM.

Attention has been called by a number of observers to a condition of the heart muscle sometimes observed, it is said, in acute infectious diseases, in acute and chronic diseases of the central nervous system, and in sudden death from a variety of causes. The muscle tissue is soft, friable, opaque, and often yellowish. Examination shows a loosening of the muscle cells from one another, as if by some change in the cement substance—*segmentation*—or the fibers may be broken across—*fragmentation*. The significance of this alteration is not yet fully established, for

[1] *Cullen, T. S.*, Bull. John Hopkins Hosp., 1906, xvii, 267.

though in some cases it is associated with degeneration and other changes in the heart muscle, in others these are not present and the alteration may be agonal, or it may in some instances be due to post-mortem changes.[1]

LESIONS OF THE CORONARY ARTERIES.

Lesions of the Coronary Arteries in Acute Infections.—It has recently been shown that in acute infectious diseases, typhoid fever, diphtheria, influenza, scarlatina, pyemia, and others, the media and the intima of the coronary arteries may be involved in necrotic and hyperplastic processes which are apparently of great significance in leading to certain forms of sclerosis of these vessels.

The coronary arteries may show, on gross examination, in both larger and smaller trunks, circumscribed, yellowish white, elevated spots, from 2 to 6 mm. in diameter, or small dull white depressions of the intima. These lesions seem to begin as a localized serous infiltration in the media which undergoes necrosis. At a later period, after recovery from the acute disease, fibrous tissue may form in the media and intima, sometimes associated with calcification. Thus a patchy form of arteriosclerosis may be developed.[2]

SCLEROSIS AND THROMBOSIS.

Obliterating Endarteritis—Sclerosis—of the coronaries, which occurs frequently, is of great significance, since diminished nutrition of the heart wall may lead to local anemia, degeneration of the muscle, fibrous hyperplasia, or aneurysm, etc.; but the formation of thrombi increases the gravity of the lesion. **Thrombosis** most commonly occurs in connection with degenerative or inflammatory processes in the coronary arteries. It may, however, be associated with occlusion of the coronary arteries at their orifices either through inflammation of the aorta in this region or by vegetations or clots on the aortic valves.

The blocking of one main trunk of the coronary arteries by a thrombus may cause death, but this is not always the case.

When through obliterating endarteritis, thrombosis, or embolus of a branch of the coronary arteries,[3] the blood supply is cut off from a circumscribed portion of the heart wall, the tissue in the affected area may undergo fatty degeneration, leading to rupture.[4] Or, instead of

[1] Consult *Hektoen*, Am. Jour. Med. Sc., 1897, cxiv, 555 (bibl.); *MacCallum*, Jour. Exper. Med. 1899, iv, 409 (bibl.); *Stamer*, Zieglers Beitr., 1907, xlii, 310; *Cohn*, Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 182 (bibl.).

[2] For a study of this lesion of the coronary arteries see *Wiesel, J.*, Wien. klin. Wchnschr., 1906, xix, 723; and Ztschr. f. Heilk., Abt. f. path. Anat., 1906, xxvii, 262; also *Wiesner, R.*, Wien. klin. Wchnschr., 1906, xix, 725.

[3] According to Sternberg, the right coronary artery supplies the following regions of the heart: most of the right auricle; the posterior part and most of the anterior part of the right ventricle; most of the interauricular and interventricular septa; the posterior part of the left ventricle and the posterior papillary muscles. The remainder of the heart is supplied by the left coronary artery.

While there are superficial anastomoses between the larger trunks of the coronary arteries, their branches do not communicate after they enter the heart muscle. For a study of coronary arteries see the monograph of *Jamin* and *Merkel*, Die Koronararterien des menschl. Herzens, Jena, 1907.

[4] Through the Thebesian vessels sufficient nutriment may reach the myocardium to maintain the muscle for a time, even with considerable lesion of the coronary arteries. See *Pratt*, Am. Jour. Physiol., 1898, i, 86; also *Baumgarten*, ibid., 1899, ii, 243. For the results of occlusion of one or more of the coronary arteries, see *Porter, W. T.*, Jour. of Physiol., 1898, xv, 121; also Jour. Exper. Med., 1896, i, 46; *Herrick, J. B.*, Jour. Am. Med. Assoc., 1919, lxxii, 387.

extensive fatty degeneration, the cutting off of the blood supply from a limited region may result in necrosis—*white infarction.* These areas, grayish in color, often slightly projecting from the surface, are frequently surrounded by a red zone of hyperemia. The nuclei of muscle and fibrous tissue fail to stain, the muscle cells become necrotic, lose their striation and degenerate, and may be absorbed or gradually replaced by fibrous tissue. When larger areas are involved, the muscle fibres may break down into a granular detritus and the connective tissue about them suffer degeneration or necrosis, so that the whole affected area may be soft and yellowish white or grayish in color. If, as not infrequently occurs, there is considerable extravasation of blood, the degenerated area may be of a dark red color.[1] Under these conditions the heart wall may rupture, or acute inflammatory processes may occur, or the degenerated muscle tissue may be gradually absorbed and replaced by granulation tissue formed from the surrounding fibrous tissue and blood-vessels. This gradually grows dense, shrinks, and assumes the characters of cicatricial tissue.

Thrombosis may occur in any part of the heart wall or in the papillary muscles, but is most common in the region supplied by the left coronary artery; that is, in the interventricular septum and the anterior wall of the left ventricle near the apex. Thrombosis of the coronary arteries is more frequent than embolism and more commonly leads to infarction. When the heart wall is involved the new-formed connective tissue may yield to the blood pressure from within and aneurysm of the heart be formed.

Impaired nutrition of a portion of the heart wall as the result of narrowing or obliteration of the coronary arteries or their branches, whether it leads to such extreme lesions as those just described, or to fatty degeneration, or to atrophy of the muscle cells with a production of new connective tissue, is of great significance, and may be the dominant factor in many cases of sudden death.

Embolism of the coronary arteries is much less common than thrombosis and may be followed by similar lesions of the myocardium. Infective emboli are freuqent excitants of suppurative lesions of the myocardium.

Aneurysm of the coronary arteries is a rare phenomenon.[2] The enlargement is most frequent near the origin of the vessels from the aorta.

INFLAMMATION.

Myocarditis.

The inflammatory changes in the walls of the heart involve primarily the interstitial tissue and blood-vessels, the muscle fibers being secondarily affected by atrophic and degenerative changes.

Interstitial myocarditis may be acute and suppurative, or chronic with the formation of new connective tissue.

Acute suppurative myocarditis may be diffuse, infiltrating the wall of the heart with pus. This may occur as a complication of infectious

[1] This condition of the heart is often called "myomalacia."
[2] *Capps*, Am. Jour. Med Sc., 1899, cxviii, 312.

diseases, such as influenza, scarlatina, diphtheria, typhoid fever, and gonorrhea,[1] or may be associated with ulcerative endocarditis.[2]

More frequently the suppurative inflammation is circumscribed, resulting in abscesses. These occur with pyemia, mycotic ulcerative endocarditis, and other infectious diseases. They are of different sizes and either single or multiple. They are produced by the lodgment of infectious emboli in small vessels. There is at first necrosis of the muscle fibers near the bacterial mass (Fig. 367), followed by local suppuration and the formation of abscess. The contents of the abscesses consist of pus, broken-down muscle tissue, and bacteria. These abscesses may open into the pericardial sac and set up a purulent pericarditis; or into a heart cavity, giving rise to thrombi in the heart and infective emboli in different parts of the body; or the wall of the heart may be weakened by the abscess so that it ruptures, or an aneurysmal sac is formed; or an abscess in the interventricular septum may establish an opening between the ventricles; or the suppurative process may extend upward and form

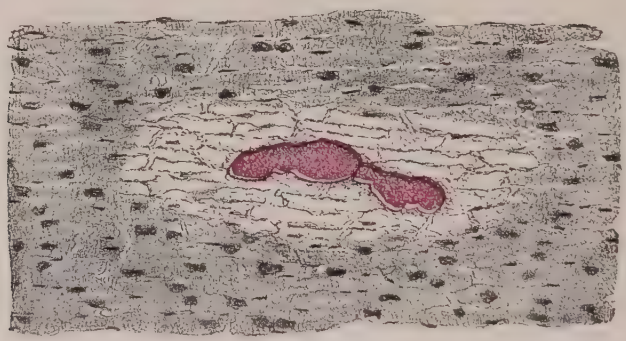


FIG. 367.—BACTERIAL EMBOLUS IN HEART MUSCLE.
The bacteria have multiplied since lodgment in the small vessel, so that the latter is widely distended. The surrounding muscle is necrotic.

an abscess in the connective tissue at the base of the heart. In diphtheria, necrosis, and hyaline or waxy degeneration of the muscle fibers are not infrequent.[3] Interstitial inflammatory collections are seen, also. Streptococcus and Staphylococcus pyogenes are the most common excitants.

In rare cases the patients recover, the contents of the abscesses become dry and hard and inclosed by a wall of fibrous tissue, or the contents may be absorbed and the whole replaced by fibrous tissue.[4]

Chronic interstitial myocarditis may be associated with chronic pericarditis or endocarditis; with chronic nephritis or it may be secondary to

[1] For a consideration of gonorrheal myocarditis, consult *Councilman, W. T.*, Am. Jour. Med. Sc., 1893, cvi, 277.

[2] For a study of experimental focalized myocarditis in relation to Aschoff nodules, see *Thalhimer* and *Rothschild*, Jour. Exper. Med., 1914, xix, 429.

[3] *Anitschkow*, Virchows Arch., 1913, ccxi, 193.

[4] For study of experimental myocarditis, see *Fleischer* and *Loeb*, Arch. Int. Med., 1909, iii, 78. For a summary of conditions under which myocarditis occurs, see *Brooks, H.*, Am. Jour. Med. Sc., 1911, cxlii, 781.

damage to the muscle by bacterial or other toxins, but in a large proportion of cases it occurs in connection with lesions of the coronary arteries.

Lesions of the coronary arteries which interfere with the blood supply of the heart muscle, such as obliterating endarteritis with or without thrombosis or embolism, may lead to degeneration or necrosis of the muscle and to a new formation of fibrous tissue which is in reality a replacement hyperplasia. Thus either in small foci or over more diffuse areas, patches of fibrous tissue may be formed as the muscle disappears (Fig. 368).

If the occlusion of the coronaries has led to infarctions of the heart, then also, as we have seen above, new fibrous tissue may form, replacing the muscle.

Local degenerative processes and necrosis in the muscle tissue of the

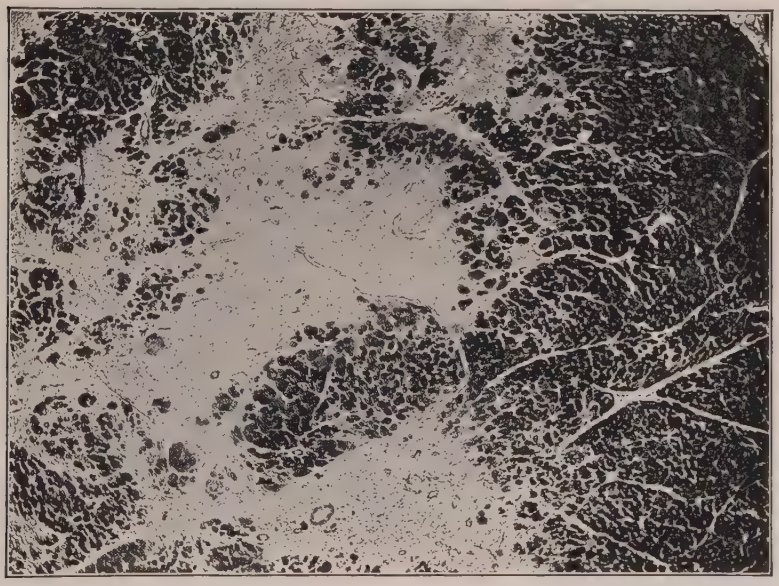


Fig. 368.—Chronic Interstitial Myocarditis (Fibrous Replacement Hyperplasia).

heart may be associated with acute infectious diseases, especially with diphtheria, typhoid fever, and scarlatina. In such areas of damaged muscle new connective tissue may form. This is at first cellular, later dense and cicatricial in character. As the result of this replacement hyperplasia, patches of fibrous tissue may be scattered through the myocardium. Similar lesions may be induced experimentally in animals by the injection of bacterial toxins.[1] Calcification of the muscle fibers has been observed in connection with the degenerative processes due to the action of toxins.[2]

[1] *Flexner, S.*, Johns Hopkins Hosp. Rep., 1897, vi, 259.

Degeneration of muscle fibers and the formation of new connective tissue has been induced in the hearts of rabbits by the injection of adrenaline into the ear vein. See *Pearce, R. M.*, Jour. Exper. Med., 1906, viii, 400.

[2] *Cullen, E. K.*, Bull. Johns Hopkins Hosp., 1906, xvii, 267.

Chronic interstitial myocarditis, whether diffuse or focal, leads to a weakening of the heart wall. This may be slight or excessive. Hypertrophy of the muscle may follow or be associated with it; degeneration of the remaining muscle may occur; or the heart wall may yield to the internal pressure and pouch, forming aneurysm of the heart. Thrombi may under these conditions form in the dilated cavities. Lack of rhythm in the heart-beats or cardiac pain—*angina pectoris*—may result from myocarditis. On the other hand, in many chronic conditions in which the heart clinically shows symptoms referable to enfeeblement of the cardiac muscle, no microscopic lesions can be made out.

FIG. 369.—CHRONIC INTERSTITIAL MYOCARDITIS.

Showing cross section of a papillary muscle. The muscle tissue is least involved about the vessels and near the surface.

It is believed by most modern observers that the new connective tissue which develops in the heart in connection with atrophy of the muscle fibers, as a result of impaired nutrition due to a narrowing of the lumen of the coronary arteries or to other causes, is not, in the stricter sense, inflammatory in its nature, but is rather a *fibrous hyperplasia*, the new-formed connective tissue forming secondarily, to replace the muscle fibers which have atrophied. Nevertheless we still for convenience call the lesion myocarditis, thus implying inflammation. It is interesting in this connection to note that under these conditions the muscle fibers immediately beneath the endocardium and close around the blood-vessels, where the nutritive supply is most abundant, are often not atrophied, nor is the growth of connective tissue marked (Fig. 369).

In almost all cases of valvular heart disease, changes in the heart muscle can be found if sufficiently extensive microscopical examinations are made. Usually these changes are in the nature of a fibrosis; but in a certain number of cases of rheumatic endocarditis, though not in all, perivascular collections of cells of an epithelioid type with large pale nuclei have been found. Some of these elements resemble plasma cells, but are probably not strictly of this type; others are of very large size, and resemble the giant cells seen in the lymph-nodes in Hodgkin's disease. Occasionally, eosinophilic and neutrophilic leucocytes may be found in small numbers. These nodules, the so-called *Aschoff bodies*, are especially abundant in the wall of the left ventricle, near the base, and in the interventricular septum.[1]

FIG. 370.—ULCERATIVE ENDOCARDITIS.
The valve and adjacent portion of the heart wall are ulcerated, and a ragged clot has formed upon the roughened surfaces.

Tuberculous myocarditis is of occasional occurrence and may be associated with tuberculosis of the pericardium or endocardium.[2]

Syphilitic Myocarditis is accompanied by the growth of connective tissue or granulation tissue in the wall of the heart between the muscle fibers or in the walls of the blood-vessels. The pericardium and endocardium may also be thickened, and pericardial adhesions may be formed. Gummata of the heart are of rare occurrence,[3] although in

[1] See *Aschoff*, Verhandl. d. deutsch. path. Gesellsch., 1904, viii, 46; and *Fraenkel, E.*, Zieglers Beitr., 1912, lii, 597.

[2] Consult *Moser*, Tuberculosis of the Heart, Boston City Hosp. Rep., 1900, 11th ser., p. 194. Also *Andres*, Jour. Am. Med. Assn., 1902, xxxix, 1081. Also *Raviart*, Arch. de méd. expér., 1906, xviii, 141 (bibl.).

[3] See *Loomis, H.*, Am. Jour. Med. Sc., 1895, cx, 389 (bibl.); *Adler*, Tr. Assn. Am. Phys., 1898, xiii, 73 (bibl.); and *Berblinger*, Centralbl. f. allg. Path., 1910, xxi, 1045 (bibl.).

recent years many more cases have been recognized because of the frequency with which the gumma produces heart block by interference with the conducting system.

ENDOCARDITIS.

The endocardium is a connective-tissue membrane, containing but few blood-vessels, which lines the cavities of the heart and forms its valves. Its inner surface is covered with a layer of endothelial cells. It is frequently subject to inflammatory changes, in which the connective-tissue cells and the basement substance are principally concerned. The new tissue thus produced is prone to degeneration and calcification. The roughening of the endocardium due to the inflammation often leads to the formation of fibrin on the affected surface.

The endocardium which forms the valves is that which is most frequently involved, but the other portions of it are by no means exempt.

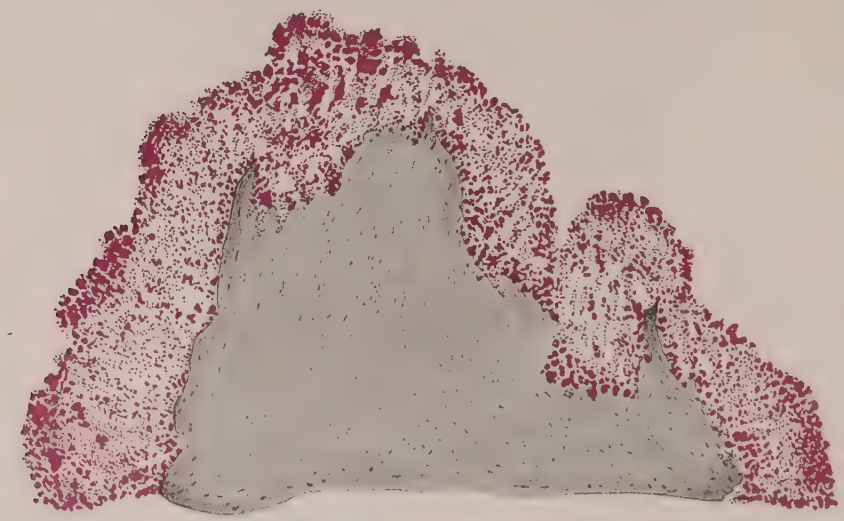


FIG. 371.—MASSES OF BACTERIA IN VEGETATION ON THE HEART VALVE IN INFECTIVE (MALIGNANT) ENDOCARDITIS.

In adult life it is the endocardium of the left ventricle, and especially of the aortic and mitral valves, which is most commonly affected. In fetal life it is the endocardium of the right heart which is usually affected.

1. **Simple Acute Endocarditis.**—This is frequent with rheumatism, but may occur under other conditions. It may occur in a heart previously healthy, or in one already the seat of chronic endocarditis.

In some cases the only lesion is a simple swelling of the valves. These are thick and succulent, but their surfaces remain smooth. The basement substance is swollen, and there is a moderate production of new connective-tissue cells. In other cases the growth of connective-tissue cells is more marked, the basement substance is split up, and little cellular fungous masses of connective tissue, called "vegetations," project

from the free surface of the endocardium. This is sometimes called *verrucous endocarditis*. On these roughened surfaces the fibrin of the blood may be deposited, and thus vegetations of considerable size may be formed (see Fig. 370). In still other cases the cell growth, while in some places forming vegetations, in other places degenerates, and thus portions of the valves are destroyed. Less frequently, the ventricular wall may be affected by the formation of small soft granular masses of fibrin, blood-plates, and leucocytes. This is *simple acute ulcerative endocarditis*. In some cases of this disease the patients recover and the valves seem to return to a normal condition; in other cases the valves are left permanently damaged; and in still others chronic endocarditis follows the acute form.

FIG. 372.—CHRONIC ENDOCARDITIS.
Section showing thickening of the cusp of the aortic valve.

2. Mycotic or Malignant Endocarditis (Malignant Ulcerative Endocarditis).—The direct excitants of simple acute endocarditis of the forms described above are unknown, but in a considerable number of cases of acute endocarditis bacteria have been found in and about the vegetations, and proved, by careful experiments, to stand in a causative relation to the lesion.

Those cases of acute endocarditis in which the lesions are induced by the direct action of bacteria are called *mycotic* or *malignant endocarditis;*

or, since the new-formed as well as the old tissue about the bacteria is apt to become necrotic and thus lead to larger or smaller losses of substance, the lesion is often called *malignant ulcerative endocarditis*. Cases of multiple aneurysm in connection with mycotic endocarditis have been reported. Various species of bacteria may be excitants of malignant endocarditis (Fig. 371).

It is most commonly induced by Staphylococcus pyogenes aureus and Streptococcus pyogenes and viridans. Diplococcus pneumoniæ,[1] B.

Fig. 373.—Chronic Endocarditis.
Showing thickening and coalescence of two of the aortic cusps.

typhosus, B. tuberculosis, B. anthracis, Micrococcus gonorrhœæ,[2] and other organisms have been occasionally found.[3] The specific organisms

[1] For a résumé of pneumococcus endocarditis, see *Preble, H. B.*, Am. Jour. Med. Sc., 1904, cxxviii, 782.

[2] For bibl. of gonorrheal endocarditis, see *Külbs*, Wien. klin. Wchnschr., 1907, xx, 11.

[3] For a general consideration of infective endocarditis, see *Washbourn*, and others, Brit. Med. Jour., 1899, ii, 1269, *Billings, F.*, Arch. Int. Med., 1909, iv, 409; and *Simons, I.*, Quart. Jour. Med., 1914, xxii, 291. For a study of the meningococcus in endocarditis, see *Warfield*, Univ. Pennsylvania Med. Bull., 1903, xvi, 180; and *Cecil* and *Soper*, Arch. Int. Med., 1911, viii, 1. For studies on bacteria in blood in "subacute" endocarditis, see *Libman* and *Celler*, Am. Jour. Med. Sc., 1910, lcx, 516; and *Libman, E.*, ibid., 1912, cxliv, 313.

can usually be demonstrated in the blood stream during life, if repeated cultures are made; but individual examinations are often negative.

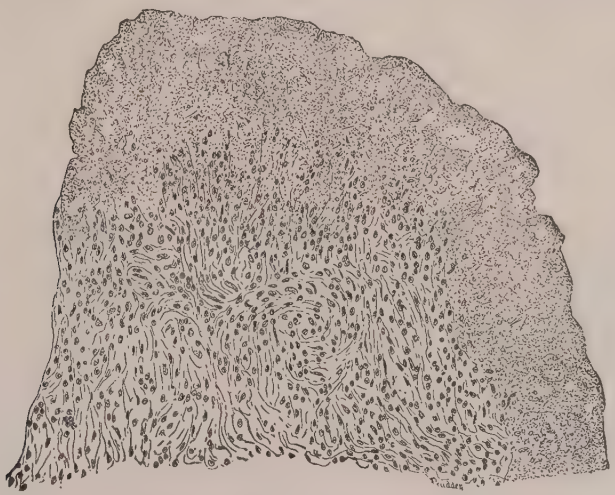


FIG. 374.—VEGETATION ON AORTIC VALVE IN ENDOCARDITIS.
Showing granular thrombus over the surface.

FIG. 375.—CHRONIC ENDOCARDITIS.
Showing fibrous "vegetation" on the mitral valve, with a large blood clot formed upon it.

It has, furthermore, been found that a lesion or injury of the endocardium, either on the heart valves or elsewhere, predisposes to the lodgment and growth upon it of pathogenic bacteria when once they have gained access to the circulating blood.

Mycotic endocarditis is frequently a secondary complicating lesion, but may occur as a primary disease. It is most apt to be associated with the acute infectious diseases, and may be one of the local manifestations of pyemia.[1]

In some cases there is a formation of new tissue in the form of organized vegetations on the valves or general endocardium; in other cases necrosis either of the new-formed or the old tissue is the most marked feature. Thrombi are apt to form on the affected surfaces and often largely make up the so-called vegetations. The mitral and aortic valves

FIG. 376.—CHRONIC ENDOCARDITIS (VERRUCOUS ENDOCARDITIS).
The new papillary growths of connective tissue involve the mitral valve and obstruct the mitral orifice.

are frequently the seat of the lesion, but it may occur elsewhere, not infrequently on the septal wall of the left ventricle.

Detachment of bacteria-containing fragments of the vegetations or clots may give rise to single or multiple infectious emboli and abscesses in various parts of the body, such as the spleen, kidneys, brain, skin, heart wall, etc. Bacteria similar to those in the heart lesion may be found in these secondary abscesses.

It is probable that abscesses in ulcerative endocarditis do not always arise from cardiac emboli, but may precede the heart lesion.

[1] For a study of local predisposing factors in malignant endocarditis, see *Prudden, T. M.*, Am. Jour. Med. Sc., 1887, xciii, 55. For experimental endocarditis, see *Rosenow, E. C.*, Jour. Infect. Dis., 1912, xi, 210.

3. Chronic endocarditis may succeed acute endocarditis, or the inflammation may be chronic from the outset. It affects most frequently the aortic and mitral valves, and the endocardium of the left auricle and ventricle, similar changes in the right side of the heart being much less frequent.

There are two main anatomical varieties of chronic endocarditis, which may occur separately or together:

1. The endocardium is thick and dense, its surfaces are smooth or covered with small, hard vegetations or ridges (Fig. 372 and 373); it is often infiltrated with the salts of lime.

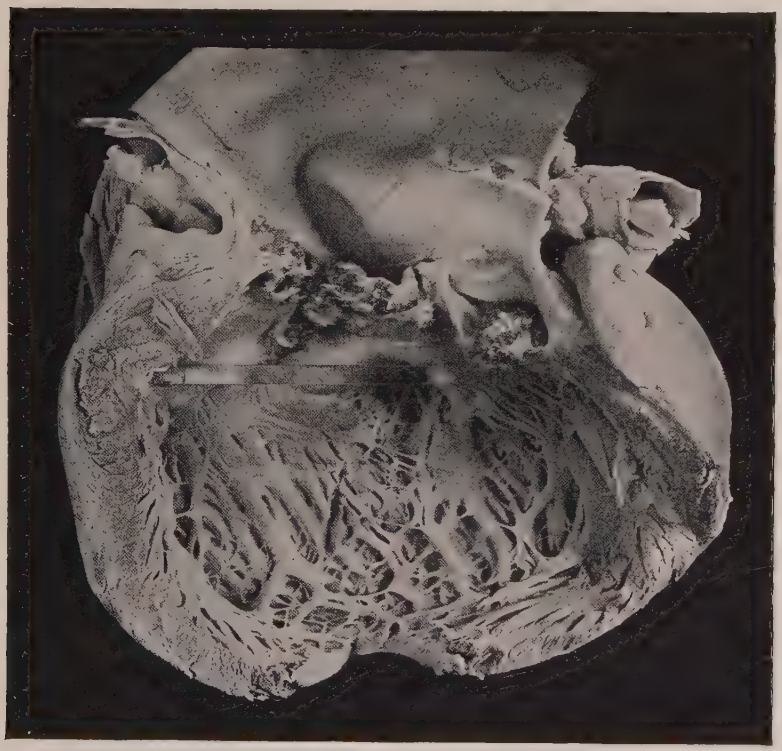


FIG. 377.—CHRONIC ENDOCARDITIS WITH CALCIFICATION OF THE THICKENED VALVES.

2. There is a growth of connective-tissue cells in the endocardium, with a splitting-up of the basement substance. Some of the new cells continue to live, others degenerate. By the combination of such a cell growth and destruction the endocardium is in some places destroyed, in others changed into projecting vegetations (see Fig. 374). Fibrin is deposited on the roughened surfaces (Fig. 375 and 376). After a time the condition may be further complicated by shrinkage and the deposition of the salts of lime in the new tissue and in the endocardium (Fig. 377). All these changes may extend to the wall of the heart beneath the endo-

cardium. As the result of the new formation of connective tissue the cusps of the valves may be shortened or grown together or adherent to the heart wall. The chordæ tendineæ may be shortened and the papillary muscle fibers shortened and distorted.

The most important result of chronic endocarditis is its effect on the heart valves, producing insufficiency and stenosis (Fig. 378). The changes in the valves are followed by changes in the walls and cavities of the heart, and disturbances of the circulation throughout the body (page 638).

4. Chronic Ulcerative Endocarditis.—Large ulcers or perforations of the valves may be formed in chronic endocarditis, upon which clots may form, so that in gross appearance a great similarity exists between this and malignant ulcerative endocarditis, particularly if the latter

Fig. 378.—Stenosis of the Aortic Valves.
In chronic endocarditis.

has been engrafted upon an already chronically diseased endocardium. Microscopical and biological examinations must usually be resorted to in order to determine the exact significance of the lesion.

5. Tuberculous Endocarditis may occur in connection with tuberculous pericarditis or general miliary tuberculosis. The tubercles may be small and single, or grouped in masses, and show the usual degenerative changes.[1]

HEART BLOCK.

The cardiac muscle beats independently of nerve control, as is shown by the rhythmic contractions of isolated strips of the muscle and by the beating of individual muscle fibers growing in plasma. The rate is influenced by impulses from the extrinsic nerves of the heart, stimulation of the vagi slowing, that of the sympathetic hastening the rate. The gen-

[1] See *Moser*, Boston City Hosp. Rep., 1900, 11th ser., p. 194; also *Etienne*, Arch. de méd. expér., 1898, x, 146.

eral control of the rate of cardiac contractions, however, lies in a small area of specialized muscle tissue surrounded by branches of the vagus and sympathetic nerves and containing a few ganglion cells. This area is known as the sinoauricular node (Fig. 379). It is situated beneath the epicardium in the groove between the right auricle and the superior vena cava. The muscle cells are smaller, the cross striations are less definite than in the heart muscle from other areas, and the cells contain more glycogen. Finally, a connection seems to exist between this node and another neuromuscular organ, known as the auriculoventricular conducting system, which begins as a small clump of cells, Tawara's or the auriculoventricular node, and continues as the bundle of His. These morphological elements lie beneath the endocardium in the lower part of the right auricle. The His bundle splits ultimately, as it ramifies down-

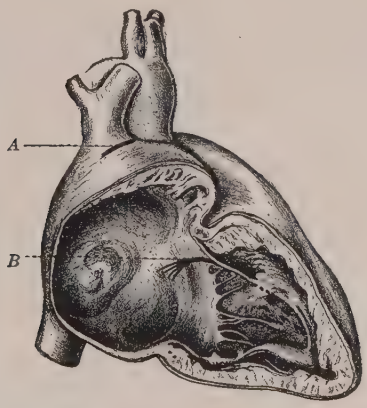


FIG. 379.—DIAGRAM OF HEART.
Showing *A*, sinoauricular node; and *B*, auriculoventricular node.

FIG. 380.—DISSECTION OF HEART.
Showing conducting bundles in the wall of the ventricle. (*Tawara.*)

ward, into two main branches, one going to the right ventricle, the other to the left. The cells resemble those of the sinoauricular node (Fig. 380).

The normal impulse of contraction arising in the sinoauricular node spreads through the auricle, reaches the junctional tissue, and from there, through the two branches of the terminal arborizations, spreads to the papillary muscles and throughout the ventricle.[1]

The condition known as heart block is found in hearts in which there is a dissociation between the action of the auricle and that of the ventricle induced by lesions which more or less completely sever the conduction system. Functional interference with this conduction system may be produced, also, by drugs, such as digitalis, and probably by tobacco; and partial heart block is not infrequently seen in various nervous and infectious diseases. A lesion often found is a syphilitic process, frequently of a gummatous nature, somewhere along the course of the con-

[1] For an admirable review of the excitatory and connecting muscular system of the heart and its relation to disease, see *Josué, O., Lewis, T.*, and *Mackenzie, J.*, XVIIth Internat. Cong. Med., 1913, Sect. III, part 1, p. 1.

ducting bundle. Tumors, calcareous deposits, inflammatory infiltration, fibrosis, and hemorrhage into the nodal tissue, also, may produce partial or complete heart block. In a certain number of cases, no microscopic lesion has been demonstrated. In removing material from suspected heart-block patients, the heart should be opened as shown on page 1208, not by the usual method.

Clinically, the disease is evidenced by great slowing in the ventricular rate. The auricle continues to beat at its ordinary speed, the ventricular contractions occur at every other, every third, or even every fourth auricular contraction. In some instances, however, the auricular speed is very high; contractions at the rate of 300 per minute have been observed, while the ventricular contractions were only 75, the so-called 1 to 4 ratio. If block is complete the ventricular contractions bear no time relation to those of the auricle.

The usual signs of heart block are slow irregular pulse, and dyspnea on exertion and weakness; when these are accompanied by attacks of syncope, epileptiform convulsions, and muscular twitchings, the condition is known as Stokes-Adams disease.[1]

HYPERTROPHY AND DILATATION OF THE HEART.

We have seen in an earlier chapter that the circulation of the blood may be impaired by deficient cardiac power, such as may result from innutrition of the muscle from general causes, or from obstruction of the coronary arteries, from degenerative changes in the muscle, faulty innervation, the action of poisons, etc.

But with unimpaired vigor of the heart muscle the circulation may be interfered with by many abnormal conditions. If the orifices of the heart are narrowed the blood is forced through them with difficulty; if the valves are defective the blood regurgitates. If there be obstruction in the vascular system the flow of blood is retarded.

Under these and many other conditions an unusual amount of work is thrown upon the heart muscle, which may adapt itself to its unusual tasks by a hypertrophy which more or less fully compensates for the difficulties of the circulation.[2] This is compensatory hypertrophy of the heart. The portion of the heart muscle especially involved in hypertrophy is determined by the location of the obstruction to the circulation. The hypertrophy is usually associated with dilatation of one or more of the heart cavities.

Hypertrophy may involve the walls of one or more or all the cavities

[1] For details of other cardiac arrhythmias and further information regarding heart block, see standard textbooks on diseases of the heart, such as *Mackenzie, J.*, Disease of the Heart, 3d ed., New York, 1914; *Neuhoff, S.*, Clinical Cardiology, New York, 1917; and *Lewis, T.*, Mechanism of the Heart Beat, London, 1911; and Clinical Disorders of the Heart Beat, London, 1912. For a summary of the cause of the heart beat, see *Howell, W. H.*, Harvey Lecture, Jour. Am. Med. Assn., 1906, xlvi, 1165, 1749. For detailed anatomy of the conducting system, see *Tawara, S.*, Das Reizleitungssystem des Säugethierherzens, Jena, 1906. For methods of recording, see *Wiggers, C. J.*, Modern Aspects of the Circulation in Health and Disease, Philadelphia, 1915.

[2] For a suggestive study of cardiac hypertrophy as an adaptive process, see *Welch*, Adaptation in Pathological Processes, Trans. Congr. of Am. Phys. and Surg., 1897, iv, 284.

For a comprehensive résumé of the normal and pathological physiology of the heart and its morphological and functional lesions, see *Heinz*, Handbuch d. exp. Path. und Pharmakol., Jena, 1905, Bd. i.

of the heart. While the wall of a ventricle is thickened, its cavity may retain its normal size—*simple hypertrophy;* or be dilated—*excentric hypertrophy;* or be contracted—*concentric hypertrophy.* Simple hypertrophy is not common, but may occur in connection with the atrophied kidneys of chronic diffuse nephritis.

Care should always be exercised in judging of cardiac hypertrophy, for a firmly contracted heart seems to have a small cavity and thick walls (Fig. 381). It should also be borne in mind that an increase in the amount of fat in and about the heart may make the organ appear larger, when there may be actually a considerable decrease in the amount of muscle tissue. The existence of such a condition as concentric hyper-

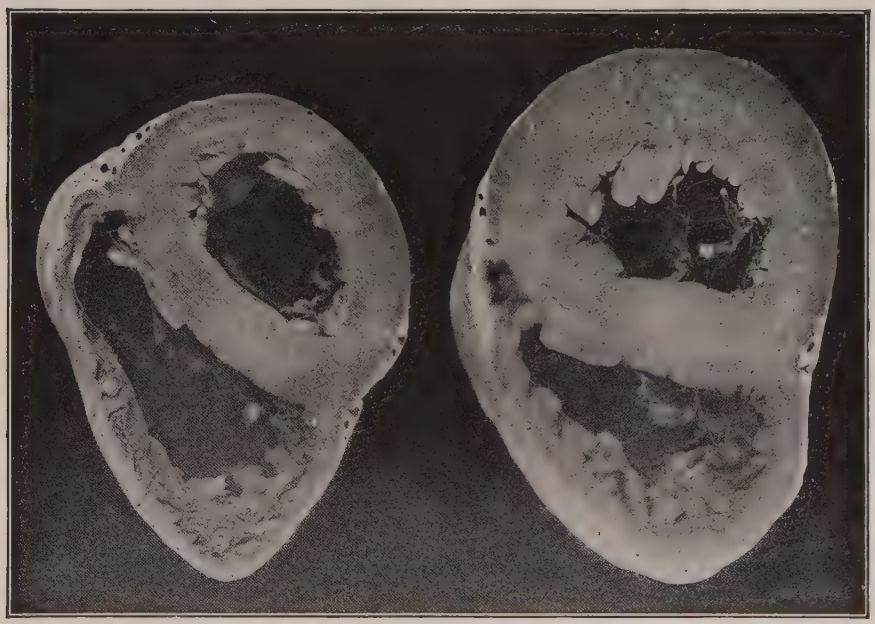


FIG. 381.—CROSS-SECTIONS OF HEART SHOWING HYPERTROPHY.
The heart at the left is normal. The heart at the right shows hypertrophy (concentric) with contraction of the left ventricle.

trophy is denied by some authors. Excentric hypertrophy is the most common form. The muscle tissue in hypertrophied hearts is firmer and denser than normal, and is apt to have a darker color. Fatty degeneration may, however, be associated with it, giving the walls a lighter appearance. It is probable that the increase of tissue in the hypertrophied heart wall is the result of increase in the size but not in the number of the muscle fibers. In extreme hypertrophy, there is, also, in some instances a moderate increase in the intermuscular connective tissue.

Hypertrophy of both ventricles increases both the length and breadth of the heart. Hypertrophy of the left ventricle (alone) increases its length. The apex is then lower and farther to the left than usual.

Hypertrophy of the right ventricle (alone) increases the breadth of the heart toward the right side; but sometimes the right edge of the heart retains its normal situation and the apex is displaced to the left. With large hypertrophy of both ventricles, the base of the heart may sink, so that its long axis approaches a horizontal direction.

Hypertrophied hearts may weigh from 1200 to 1500 grams, or even more.

Hypertrophy of the heart may depend upon a variety of conditions which increase its work; of these, chronic arteriosclerotic changes in the kidneys are the most frequent.

LESIONS OF THE HEART VALVES IN RELATION TO HYPERTROPHY AND DILATATION.

As the result of acute infective processes in the endocardium the heart valves may undergo numerous changes. These are most frequent in connection with acute articular rheumatism, various forms of septicemia, typhoid fever, scarlatina, gonorrhea, etc. We have already seen in detail the alterations induced in infections of the endocardium. As the result of these and other processes the heart valves suffer ulceration, thrombosis, adhesions, distortions; the chordæ tendineæ may be shortened or the papillary muscles deformed; while the orifices may be less exactly controlled than normally as the result of myocardial lesions. Thus it frequently occurs that the orifices of the heart are too narrow or the valves close imperfectly, or both conditions are present together.

The narrowing of the orifices is called *stenosis;* the failure of the valves to close properly is called *insufficiency.*

AORTIC INSUFFICIENCY AND STENOSIS.

In *insufficiency of the aortic valves* the blood which has been sent forward into the aorta by the contraction of the left ventricle in part returns to the ventricle in the following diastole through the incompletely closed aortic orifice. This, unless the ventricle wall adapts itself to the changed conditions, may lead to an interference with the entrance of blood from the left auricle and so to pulmonary congestion. Under these conditions, then, of aortic insufficiency more work is thrown upon the muscle of the left ventricle, which may undergo compensatory hypertrophy. With this there is usually associated a dilatation of the ventricle cavity on account of the larger amount of blood which it is forced to accommodate.

Syphilis is a frequent inciting agent in this valvular lesion, especially in young men. The disease may show itself within a year or two after infection, and anginal symptoms are frequent, being due, in many instances, to an aortitis. Dilatation of the aorta is an additional factor and is present in many syphilitics without any vascular or cardiac symptoms. In old persons, the lesion is more frequently due to a non-specific arteriosclerotic retraction of the valves.

In *stenosis of the aortic valves* there is obstruction to the passage of the blood into the aorta, and the muscle of the left ventricle is forced to do so much extra work that the wall of the ventricle becomes hypertrophied. This hypertrophy may be followed by dilatation of the ventricle through a subsequent weakening of the wall.

MITRAL INSUFFICIENCY AND STENOSIS.

In *mitral insufficiency* a part of the blood during systole of the left ventricle is forced back into the auricle. As the result of this the auricle is forced to do more work; its wall undergoes more or less hypertrophy and dilatation. Under these conditions the blood cannot properly flow from the pulmonary veins, which become congested. This in turn brings more work upon the right ventricle, which undergoes hypertrophy. But when the diastole of the left ventricle occurs, blood flows into it from the auricle and the pulmonary system under increased pressure, while it is forced to do more work in systole to compensate for the backward current through the faulty mitral valve. Thus the wall of the left ventricle becomes hypertrophied and at the same time becomes dilated from the increased amount of blood which it is forced to accommodate.

In *mitral stenosis* the flow of blood from the left auricle into the left ventricle is obstructed so that more work must be done by the muscle of the wall of the auricle. This undergoes a certain amount of hypertrophy and also of dilatation on account of the increased pressure in the pulmonary veins. For the pulmonary vessels become overfilled owing to the resistance which the blood encounters in the obstructed mitral orifice. The heightened pressure of the pulmonary vessels is felt in the right ventricle, which must do more work, and undergoes hypertrophy.

As to the left ventricle, the wall may remain unaffected in uncomplicated mitral stenosis or may suffer degenerative changes or atrophy if the right heart fails to compensate properly for the obstructive lesion.

INSUFFICIENCY AND STENOSIS IN THE RIGHT HEART.

We need not trace these lesions of the right side of the heart in detail, for the changes are quite similar in principle to those which we have just considered. But they are by no means as frequent or as pronounced, nor is the compensatory mechanism as perfect as in the left heart. Lesions of the valves of the right heart are less frequent than those of the left. Tricuspid lesions infrequently develop in adult life. Lesions of the pulmonary valves developing in the adult are rare. During fetal life, however, lesions of both of these valves are not infrequent. Congenital heart lesions, such as stenosis of the pulmonary artery, may lead to hypertrophy of the right ventricle.

While we have thus briefly touched upon some of the more common and obvious of the conditions associated with the lesions of one or the other of the heart valves, there are many intricacies and variations for

the details of which we must refer to special works on the subject.[1] But we should remember that there are frequent combinations of valvular lesions on both sides of the heart. Thus simple mitral insufficiency is common, while uncomplicated mitral stenosis or aortic insufficiency or stenosis is less frequent than are combinations of insufficiency with stenosis in either the mitral or aortic valves.

SUMMARY OF CONDITIONS LEADING TO HYPERTROPHY OF THE VENTRICLES.

Hypertrophy of the Right Ventricle.

This occurs especially under conditions which lead to increased resistance to the flow of blood in the pulmonary vessels, for example, in interstitial pneumonia, pulmonary tuberculosis, emphysema with chronic bronchitis and pleuritis, rarely with sclerosis of the pulmonary artery or incompetence or stenosis of the pulmonary or tricuspid valves. But lesions of the mitral valve or lesions of the wall of the left ventricle interfering with the pulmonary circulation may indirectly lead to hypertrophy of the right ventricle.

Hypertrophy of the Left Ventricle.

Aside from the valvular lesions already considered, hypertrophy of the left ventricle may arise from stenosis or aneurysm of the aorta, from an increased resistance of the flow of blood through the peripheral arteries as in various forms of obliterating endarteritis or arteriosclerosis, and from certain forms of diffuse nephritis.[2]

Arteries whose walls are stiffened from new-formed tissue or from degeneration or calcareous infiltration, or whose lumina are obstructed through obliterating endarteritis, do not so readily dilate as those in normal condition, nor do they promptly and readily recover when the heart pressure is reduced in diastole. Thus it is that, since the elasticity of the arteries is an important factor in the maintenance of the circulation, more work in the conditions above indicated is thrown upon the heart, which may lead to its hypertrophy.

The relationship of arteriosclerosis to hypertrophy of the heart is most complex and the results of recorded observations are conflicting. One of the chief reasons for this uncertainty is doubtless the crude method of determination of both the degree and seat of the hypertrophy and the character and grade of the arterial lesion. The common method of determining hypertrophy of the heart by simple inspection or by measurement of the thickness of the heart wall is essentially faulty because no account is taken of the degree of contraction of the muscle wall of the heart which makes the greatest difference in its thickness. Only by the

[1] See *Krehl*, Clinical Pathology, English trans. by Hewlett, 2d ed., Philadelphia, 1907; *Stadler*, Ergebn. d. Med. u. Kinderheilk., 1910, v, 1; *Mackenzie, J.*, Diseases of the Heart, 3d ed., New York, 1914; and *Norris, G. W.*, Studies in Cardiac Pathology, Philadelphia, 1911 (beautiful photographs of various heart lesions).

[2] For an experimental study of hypertrophy of the left ventricle with diminished kidney substance see *Pässler* and *Heineke*, Verhandl. d. deutsch. path. Gesellsch, 1905, ix, 99.

method of W. Müller, in which, after the removal of the fat about the heart, the muscle wall of each cavity is separated and weighed and the weight of each part compared with the weight of the whole heart, and its proportional weight to that of the whole body, or by some similar method, can exact data be obtained.[1]

Furthermore, the full significance of arteriosclerosis can be determined only by the more exact methods suggested by Thoma.[2]

The arterial lesions which appear to be of most significance in relation to hypertrophy of the heart are those of the upper aorta and those of the splanchnic system.[3] To what extent the association of kidney lesions and hypertrophy of the heart are dependent upon arterial lesions can be determined only by the accumulation of data by the more exact methods above indicated.

Hypertrophy of Both Ventricles from General Conditions.

Hypertrophy of the heart may accompany any condition which leads to a prolonged increase in the rapidity of its contractions. It may accompany exophthalmic goiter. It may be associated with severe or persistent muscular exertion, or excesses in beer-drinking or other indulgences. It may be associated with chronic pericarditis with adhesions. With the hypertrophy arising under these general conditions there may be also varying degrees of dilatation.[4]

The Limitations of Compensatory Hypertrophy.

While the hypertrophy of the heart may for a longer or shorter time measurably compensate for the various disturbances of the circulation which have been considered, it is by no means always a perfect or permanent adaptive measure.

Excessive functional demands upon the heart, interstitial myocarditis, which may have preceded the hypertrophy or followed it, degeneration of the muscle, dilatation of the cavities, obliterating inflammation and degeneration of the coronary arteries, singly or in various combinations, may in hypertrophied as in other hearts lead to irreparable damage to the organ.

DILATATION OF THE HEART.

In certain valvular lesions of the heart, as stated above (page 638), there occurs a dilatation of the heart cavities associated with hypertrophy of the muscle. This provides for the larger amount of blood which the cavities are obliged to receive and propel, and is thus compensatory and conservative. This is called *active dilatation*. On the other hand

[1] See *Müller*, Die Massenverhältnisse des menschl. Herzens, 1883; also summary by *Hasenfeld*, Deutsch. Arch. f. klin. Med., 1897, lix, 205; and *Hirsch*, Deutsch. Arch. f. klin. Med., 1900, lxviii, 55 and 321.

[2] *Thoma*, Virchows Arch., 1886, civ, 209, and following volumes.

[3] See *Hasenfeld*, Deutsch. Arch. f. klin. Med., 1897, lix, 205.

[4] *Howard's* table of 105 cases of cardiac hypertrophy shows its association with arteriosclerosis in 59 per cent.; with nephritis in 13.4 per cent.; with valvular lesion in 12.4 per cent. Johns Hopkins Hospital Rep., 1894, iii, 265.

there may be no increase of muscle tissue, but a thinning of the walls proportionate to the dilatation of the cavity—*passive dilatation.*

Either one or all of the heart cavities may be dilated, the auricles most frequently; next the right ventricle; least often the left ventricle.

Active dilatation has been already considered with hypertrophy.

Passive dilatation may be associated with:

1. Changes in the valves. Mitral or aortic stenosis or insufficiency may lead to dilatation of the auricles and right ventricle. Pulmonary stenosis or insufficiency may lead to dilatation of the right auricle and right ventricle. Aortic insufficiency, with or without stenosis or mitral insufficiency, may lead to dilatation of the left ventricle. Dilatations under these conditions are often succeeded and compensated for by hypertrophy of the heart walls.

2. Changes in the muscle tissue of the heart walls. Serous infiltration from pericarditis, myocarditis, fatty degeneration and infiltration, atrophy of the muscle fibers, may all lead to dilatation.

3. A heart which is already hypertrophied may, as we have seen, from degeneration of the muscle, become dilated.

4. Acute exudative inflammation of the lungs and acute pleuritic exudations by rendering a large number of vessels suddenly impermeable to the blood current, may produce sudden stasis in the pulmonary artery and dilatation of the right heart.

5. There are curious and often serious cases of acute and chronic dilatation of the ventricles for which no mechanical explanation is found.

TUMORS.[1]

One of the most common among the rare primary growths of the heart is the **myxoma.**[2] There is considerable doubt, however, regarding the true nature of this lesion,[3] for while it is regarded by some as a true neoplasm,[4] others describe it as an organized thrombus or inflammatory proliferation, and still others[5] refer it to congenital syphilis and describe it as a **myxogumma.**

Other benign growths of the heart or its valves[6] are **fibroma, lipoma,**[7] **hemangioma,**[7a] and **cavernous angioma.**[8] Many of the so-called tumors of the valves, however, are to be viewed with suspicion;[9] some are undoubtedly examples of *Lambl's excrescences*[10]—non-vascular papillary

[1] For a résumé of cardiac tumors in man, see *Hagedorn*, Centralbl. f. Path., 1908, xix, 825 (bibl.); in animals, see *Magnusson*, Ztschr. f. Krebsforsch., 1915, xv, 212. For a discussion of the clinical aspect, see *Meroz*, Internat. Clin., 1917, iv, 231; *Napp*, Ztschr. f. Krebsforsch., 1905, iii, 282; *Link*, Ztschrift. f. klin. Med., 1909, lxvii, 272 (bibl.).

[2] *Brenner*, Frankfurt. Ztschr. f. Path., 1908, i, 492 (bibl.); *Louria*, Proc. New York Path. Soc., 1917, xvii, 85.

[3] See *Thorel*, Lubarsch-Ostertag, Ergebn, d. allg. Path., 1907, xi^2, 442; ibid., 1903, ix^1, 901 (bibl.); and *Wegelin*, Frankfurt. Ztschr. f. Path., 1912, ix, 97.

[4] *Hanser*, Frankfurt. Ztschr. f. Path., 1911-12, ix, 362 (bibl.); *Ribbert*, ibid., 1910, iv, 30 (bibl.).

[5] *Warthin*, Jour. Infec. Dis., 1916, xix, 138.

[6] See *Hagedorn*, Centralbl. f. allg. Path., 1908, xix, 825 (bibl.).

[7] *Brewis*, Lancet, 1905, ii, 829.

[7a] For bibliography see *Timme*, Cleveland Med. Jour., 1915, xiv, 453.

[8] *Manifold*, Lancet, 1915, ii, 1027; *Schuster*, Virchows Arch., 1914, ccxv, 335 (bibl.).

[9] *Wegelin*, Frankfurt. Ztschr. f. Path., 1912, ix, 97; *Thorel*, Lubarsch-Ostertag Ergebn. d. allg. Path., 1907, xi^2, 442.

[10] *Koechlin*, Frankfurt. Ztschr. f. Path., 1908, ii, 295 (bibl.).

projections of hyaline material interspersed with connective tissue and degenerated elastic fibers, and covered with endothelium.

A few cases of **sarcoma** have been recorded, most of them spindle-cell,[1] though giant-[2] and round-cell[3] growths have been described.

For **rhabdomyoma** of the heart see pages 431 and 1136.

Metastatic tumors, both sarcoma and carcinoma, are about as rare as primary neoplasms.

PARASITES.

Echinococcus sometimes occurs in the heart wall and may perforate into the cavities. **Cysticercus cellulosæ** has been observed.

The Blood-Vessels.

HYPOPLASIA, ATROPHY, AND HYPERTROPHY.

Hypoplasia.—The aorta and larger vessels are sometimes disproportionately small as a congenital condition—hypoplasia—in which the heart may also share.[4] This condition may be associated with status lymphaticus (page 500), and may accompany chlorosis.

Atrophy of the blood-vessels may involve the entire trunk or some of its elements. It may occur as a part of general malnutrition of the body, or in connection with atrophy of particular organs, or as an accompaniment of various diseases of the vessels themselves.

Hypertrophy, which is especially seen in the arteries, may occur in the establishment of a collateral circulation upon the closure of arterial trunks; or it may occur as the result of increased blood pressure, as in some forms of hypertrophy of the heart, or from overwork. While all the coats of the vessel may be involved in hypertrophy the media is apt to be especially affected. This is seen in chronic diffuse nephritis. The hypertrophied media is liable to degeneration and weakening leading to arteriosclerosis (page 652).

The Arteries.

RUPTURE AND WOUNDS.

The arteries are predisposed to rupture by fatty degeneration, in arteriosclerosis with atheroma, and in various forms of acute inflammation.[5] Stenosis of the aorta may be followed by rupture between the occlusion and the heart. The rupture may be complete or a dissecting aneurysm may form (page 659). Rupture of the aorta may lead to sudden death (Fig. 382). There may be partial or complete rupture of an artery from contusions, wrenchings, falls, etc. The injury to an artery

[1] *Sternberg*, Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, 356.
[2] *Fraenkel*, München. med. Wchnschr., 1901, xlviii, 648.
[3] *Binder*, Frankfurt. Ztschr. f. Path., 1914, xv, 194 (bibl.); *Drysdale*, Tr. Path. Soc., London, 1903, liv, 311.
[4] For a study of hypoplasia of the arterial system, see *von Ritoók, S.*, Ztschr. f. klin. Med., 1907, lxi, 32.
[5] For a study of perforations of aorta in pyemia, see *Witte, J.*, Zieglers Beitr., 1905, xxxvii, 151.

from a penetrating wound may be fatal if the vessel is large. The wound of a small artery may close or a false aneurysm may develop at its seat.

In the healing of a wounded artery the vessel retracts and contracts, and a thrombus is formed within it. The contraction alone may be sufficient to close the vessel; its coats thicken, and the inner surfaces finally are fused together; or the blood coagulates and forms a thrombus in the vessel near the wound. This thrombus later becomes organized and the vessel is converted into a fibrous cord.

FIG. 382.—TRANSVERSE RUPTURE OF THE AORTA. (Traumatic.)

DEGENERATION.

Fatty Degeneration.—This may occur in the walls of otherwise unaltered vessels, or in those which have undergone a variety of inflammatory or degenerative changes. It may occur either in the intima or media, or both, and may be so extensive as to form a very prominent

gross lesion, or so little developed as to require the microscope for its recognition. When it is marked, especially if in the intima of large vessels, smaller and larger spots or stripes or patches may be seen, of a yellowish white color, usually sharply circumscribed, and sometimes smooth, sometimes roughened on the surface. It is most apt to occur in the aorta, but may be found in any of the vessels. In moderate degrees of the lesion we find on section that the cells of the intima contain fat droplets in greater or less number. Many of these fat droplets are double refracting, which shows that they are cholesterin esters and not true fat. When further advanced, not only are the cells crowded with fat droplets, but the intercellular tissue also may be more or less densely infiltrated with them. Sometimes the infiltration is so dense that the tissue breaks down, and there may be an erosion of the surface, forming a so-called fatty ulcer. When the media is involved the muscle cells contain fat droplets. Fatty degeneration may lead to the formation of aneurysm or to rupture of the vessels.

Amyloid degeneration, which may affect all the coats of the arteries, but especially the intima and media, has already been described in general (page 61). It will be further considered under the lesions of the organs in which it most commonly occurs.

Hyaline degeneration may cause thickening of the intima of the blood-vessels by its conversion into or infiltration with a homogeneous matter somewhat similar to amyloid (page 61); or it may involve the entire wall of smaller vessels, converting them into irregular lumpy cords. The lumen of vessels thus changed may be obliterated or occluded by thrombi.

Calcification usually occurs in vessels otherwise diseased, and may involve either the intima or media. It consists in the deposition of salts of lime either in the cells or intercellular substance. The lime may be in the form of larger or smaller granules or in dense translucent plates.

INFLAMMATION.

Acute Arteritis.—Acute inflammation of the walls of the arteries is, in the majority of cases, the result of injury, or of an inflammation in the vicinity of the vessels, or of the lodgment within them of some foreign body of an irritating or infectious nature. The inflammatory process may be largely confined to the inner coat of the vessels—*endarteritis;* or it may commence in the outer coats—*periarteritis;* or it may involve the entire wall.

The blood-vessels in the outer coats may be congested, the tissue edematous and infiltrated with pus cells and the entire wall may become necrotic. The intima, if this layer be involved, loses its natural gloss, looks dull yellowish, and is swollen, and may then ulcerate. Under these conditions thrombi usually form, and in these may occur the various changes which have been already described (page 35). But the process may originate in an infective thrombus or embolus, most commonly associated with Streptococcus or Staphylococcus pyogenes—*thromboarteritis —embolic arteritis.*

In cerebrospinal meningitis, whether this be incited by the meningococcus, streptococcus, pneumococcus, or tubercle bacillus, there may be an acute endarteritis characterized by the accumulation of leucocytes and polyhedral cells beneath the endothelium, often raising this layer from the underlying tissue (Fig. 136 and 137, page 261). This lesion may occur with or without the involvement of the outer layers of the vessel.[1]

Rupture of the artery with more or less extensive hemorrhage may follow acute suppurative and necrotic inflammation of these vessels.

FIG. 383.—THROMBOANGIITIS OBLITERANS.
Late stage with canalization of the organized thrombus.

Thus false aneurysms (page 659) may be formed. Or true aneurysms may be developed at the weakened point. In healing, fibrous tissue may form, leading to various phases of arteriosclerosis. Finally, as the result of organization of thrombi (page 38), which may be present, new tissue may form within the lumen of the involved vessel—*thromboarteritis proliferans*.

A special form of acute or subacute arteritis is seen almost exclusively

[1] For a study of this lesion of the subendothelial layers of the arteries in tuberculosis, see *Hektoen, L.*, Jour. Exper. Med., 1896, i, 112; in cerebrospinal meningitis, see *Flexner, S.*, ibid., 1907, ix, 142; in typhoid fever, see *Thayer, W. S.*, Bull. Johns Hopkins Hosp., 1904, xv, 323. For a study of arterial lesions and infectious disease, see *Frothingham, C.*, Arch. Int. Med., 1911, viii, 153.

in Polish, Galician, and Russian Hebrews, affecting the lower extremities.[1] This *thromboangiitis obliterans*, as it has been termed, begins as an acute inflammatory process with the formation of red thrombi, most frequently in the arteries, but occasionally in the veins. In some of the thrombi, purulent foci may develop, suggesting that the disease is of a microbial nature. In the later stages, the thrombi become organized, and in the new connective tissue giant cells may occur about the areas of necrosis. In the last stages, all vestiges of the acute process disappear and the thrombi become converted into vascularized connective tissue (Fig. 383). The wandering cells disappear from the media, adventitia, and perivascular connective tissue; and an obliterated, canalized, and adherent vessel is left as the final product. Most of the process is confined within the elastic lamina, though this may be very much broken up and fragmented, and an acute inflammatory infiltrate may collect in the muscularis and adventitia. The elastic tissue is, however, less affected than in the ordinary obliterating endarteritis.

The nerves of the affected extremities show considerable connective tissue proliferation about the bundles, thickening of the perineurium, and occasionally atrophy of the fibers when the lesion is extensive.

While the arteries are most frequently attacked, the deep veins are involved in about 40 per cent., and the superficial veins of the upper and lower extremities in about 20 per cent. of the cases. The venous thrombosis is in some instances recurrent, involving the different groups of vessels and simulating thrombophlebitis migrans.

Clinically, thromboangiitis obliterans is accompanied by intermittent limping,[2] pains in the muscles, with or without vasomotor symptoms, and, ultimately, gangrene. Glycosuria is occasionally present, or the sugar tolerance is very much reduced. While the Wassermann reaction is not infrequently positive in these cases, there is no evidence that the lesion is syphilitic in origin. Some observers have thought that the excessive use of tobacco might have a relationship to the disease, but there is no definite proof of this.

Arteriosclerosis (Chronic Arteritis).—Since the publication of the studies of Gull and Sutton[3] on arteriocapillary fibrosis, attention has been every year more and more directed to chronic pathological changes in the arteries as of great frequency and importance. These changes are productive and degenerative in character and have an important bearing upon the circulation and upon the integrity of the vessel walls. They are in part primary, in part secondary, and may involve single vessels or vascular territories or may affect the entire vascular system.

The lesions differ somewhat in the small and large vessels. In very small arteries there is a more or less general though not uniform thickening of the intima (Fig. 384 and 385). This is due in part to a prolifer-

[1] *Buerger, L.*, Am. Jour. Med. Sc., 1908, cxxxvi, 567; 1917, cliv, 319; Surg., Gynec., and Obst., 1914, xix, 582; and *Erb*, München. med. Wchnschr., 1910, lvii, 1105, 1181, 2450.

[2] This syndrome may be due to a chronic arteriosclerotic disease of the vessels, as well as to thromboangiitis obliterans. For a full discussion of intermittent limping, see *Cassirer, R.*, Levandowsky, Handb. d. Neurologie, Berlin, 1914, v, 291 (bibl.).

[3] *Gull* and *Sutton*, Arteriocapillary Fibrosis, Med.-Chir. Tr., London, 1872, lv 273; Brit. Med. Jour., 1872, i, 256.

ation of the endothelium, in part to increase in the connective tissue of the intermediary layer. In this way a considerable amount of moderately cellular fibrous tissue (Fig. 386) may form within the membrana elastica, and the lumen may be largely or wholly obliterated—*obliterating endarteritis*. The middle coat as well as the inner may be thickened (Fig. 387).

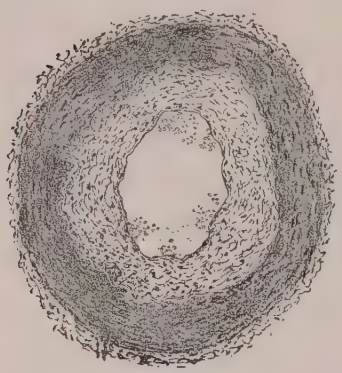


FIG. 384.—CHRONIC ARTERITIS—ARTERIOSCLEROSIS—OBLITERATING ENDARTERITIS.

Showing a thickening of the intima in a small artery of the brain.

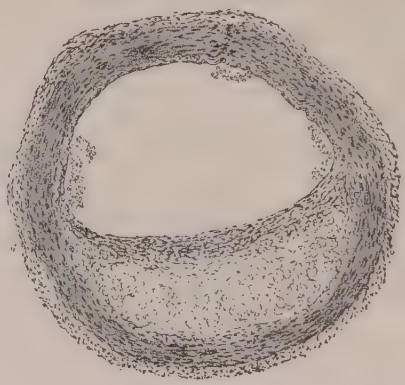


FIG. 385.—CHRONIC ARTERITIS—ARTERIOSCLEROSIS—OBLITERATING ENDARTERITIS.

The new-formed tissue is most abundant at one side of the vessel, where the external coats are pouched. There is degeneration of the new-formed tissue.

In larger arteries the new tissue may form beneath the endothelium diffusely or in circumscribed masses, or may encircle the vessel. The endothelium over the involved areas may remain intact or it may proliferate or become fatty or necrotic. The new-formed fibrous tissue of the intima, which may contain also new elastic fibers,[1] is usually dense, having few cells, and is prone to undergo fatty degeneration, to become necrotic, and to disintegrate, and thus larger and smaller cavities, filled with disintegrated tissue, fat, lipoids, and cholesterin crystals, may develop in the new-formed tissue (Fig. 385 and 388). These are called *atheromatous cysts*.[2] They may extend toward the lumen of the vessels, into which they may open, giving rise to emboli and forming rough-edged ulcers, often with undermined edges. Upon these thrombi may form. In the new-formed tissue of the intima, as well as in the necrotic foci and in the detritus of the cysts, calcification may occur.

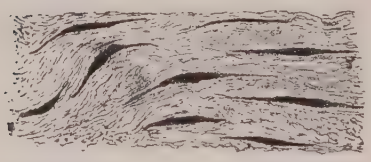


FIG. 386.—CONNECTIVE TISSUE FORMED IN THE INTIMA IN ARTERIOSCLEROSIS.

Fatty degeneration, atrophy, and calcification may occur in the muscularis and adventitia of the involved vessels. There may be degeneration, fragmentation, and atrophy of the elastic laminæ. A frequent

[1] See *Jores, L.*, Zieglers Beitr., 1898, xxiv, 458 (bibl.).

[2] The word atheroma is sometimes applied to the whole process of arteriosclerosis, designating it as atherosclerosis, but it would be well to limit it to the degenerative phases which result in softening of the tissues.

form of sclerosis in the vessels of the lower extremities is that in which the main process is calcification of the media.[1] The recognition of this type of arteriosclerosis has become more frequent with the general use of the

FIG. 387.—OBLITERATING ENDARTERITIS.
Complete occlusion of the lumen followed by gangrene of the toe. There is also fibrous thickening of the muscular coat.

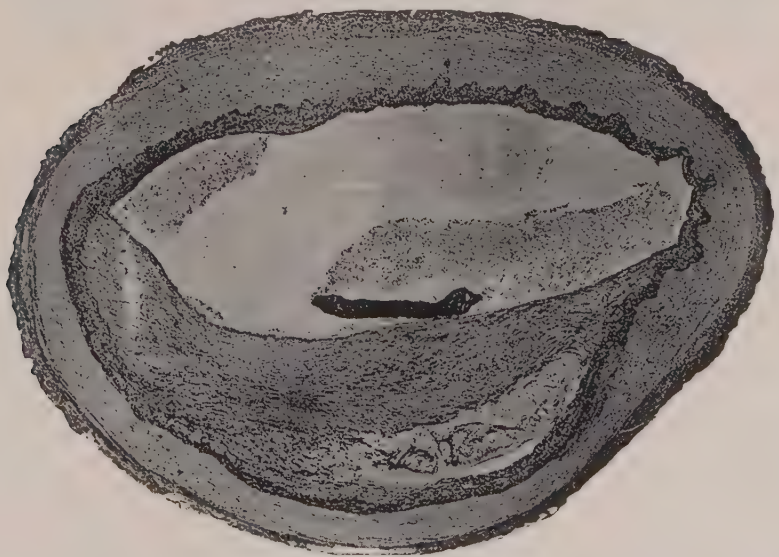


FIG. 388.—CHRONIC ARTERITIS—ARTERIOSCLEROSIS—CEREBRAL ARTERY.
Inner coat thickened; degeneration and softening (atheroma) of a part of the thickened area.

x-ray, the calcified arteries absorbing nearly as much light as the bone and appearing as clear shadows. The lime salts are deposited in ring-

[1] *Mönckeberg, J. G.*, Virchows Arch., 1903, clxxi, 141; 1914, ccxvi, 408.

like collections so that the opened artery somewhat resembles a miniature trachea. The nodules lie outside the internal elastic lamellæ in the medial layers; they may undergo transformation into true bone. The lumen of the vessel is, as a rule, not greatly compromised except in the late stages. If the intima is diseased, it is difficult to distinguish the changes from those of an advanced stage of arteriosclerosis. The lesion is often coincident with diabetes, and is probably responsible for much of the gangrene of the lower extremities which occurs in that disease, and also for some of the forms of gangrene seen in senility.

Similar processes may occur in the aorta, the new tissue growth and the degeneration being less definitely limited to the inner layer of the wall. The elastic laminæ may be degenerated, partially atrophied, fragmented, or

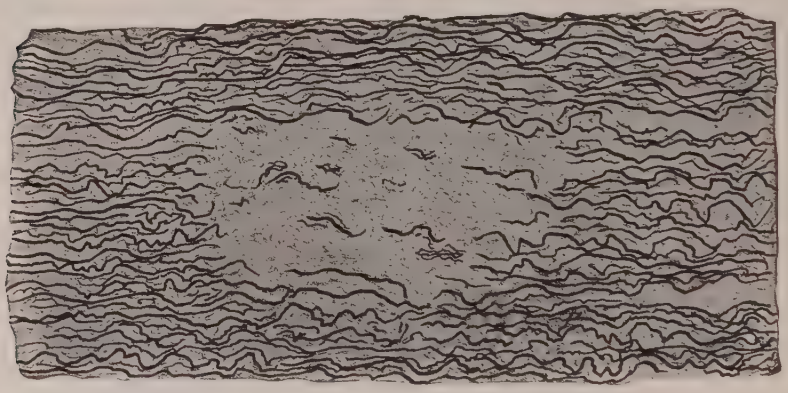


Fig. 389.—Atrophy of Elastic Tissue in Wall of the Aorta in Atheroma. The elastic tissue is replaced by dense fibrous tissue.

absent, in patches in the wall of the vessel (Fig. 389). The aorta may thus be beset with larger and smaller, irregular, white, hard, elevated thickenings (Fig. 390), often yellowish from fatty degeneration. Beneath these there may be atheromatous softening, or these sclerotic areas may be calcified and project as hard, often brownish plates with smooth or rough edges. True bone with marrow has occasionally been seen. The surface of the aorta may be rough from erosion over the degenerated areas, and upon these or elsewhere parietal thrombi may form (Fig. 391). Such sclerotic areas are often well marked at the junction of smaller vessels with the aorta.

We have seen that in the smaller vessels arteriosclerosis may lead to extreme narrowing or occlusion of the lumen. When this does not occur, and especially in the medium-sized arteries, since the new tissue is less elastic than normal and liable to yield to the pressure of the blood, the lumen may in places be dilated (Fig. 392) or the wall may rupture. In this way aneurysms may form. This is especially apt to occur when atheromatous degeneration has taken place and the muscularis is either atrophied or degenerated. In the aorta also dilatation and rupture may occur.

Arteriosclerosis may be largely limited to the aorta or to other single vessels, or it may occur in special vascular tracts, such as those of the brain or heart.

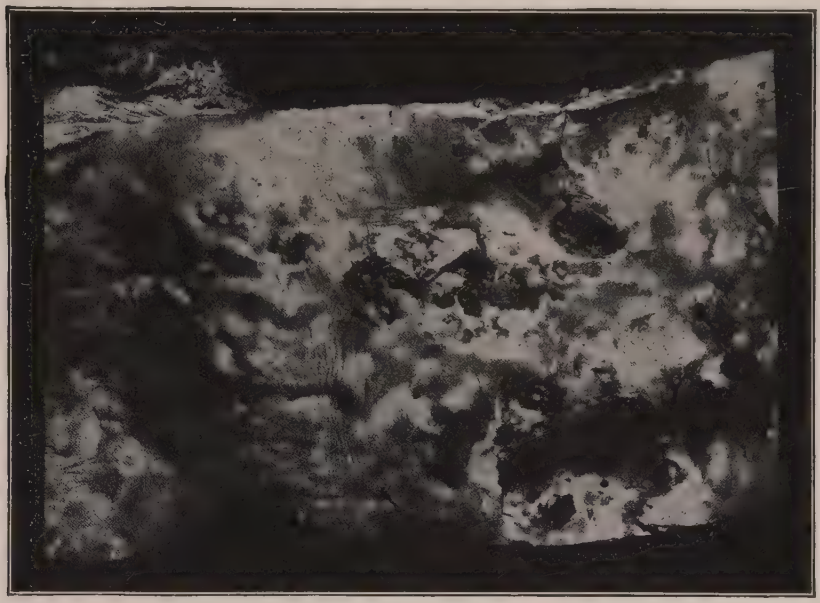


FIG. 390.—ATHEROMA OF THE AORTA.
There are fatty degeneration, thickening of the intima, calcification, and erosion. Thrombi have formed over the roughened surface of the erosions.

As the result of arteriosclerosis a great variety of circulatory disturbances may arise, both local and general. The effect upon the heart

FIG. 391.—CHRONIC INFLAMMATION OF THE AORTA—ATHEROMA OF THE AORTA.
Section showing involvement of all the layers. The thickening of the intima is irregular, and areas of degeneration are seen in its deeper portion. Patches of fibrous tissue are present in the muscularis. A small thrombus has formed upon the surface.

of the narrowing of the lumen of the arteries, as well as the loss of their elasticity, has been discussed above (page 640).[1]

[1] For a comprehensive résumé of the normal and pathological physiology of the blood-vessels, see *Heinz*, Handbuch d. exp. Path. und Pharmakol, Jena, 1905, Bd. ii.

The Conditions Leading to Arteriosclerosis.—The lesions of arteriosclerosis often occur with gout, syphilis, diabetes, chronic lead and alcohol poisoning, overwork, and overfeeding. They are usual in senility,[1] and predisposition to them may be inherited. They may be associated with cardiac hypertrophy from valvular lesions or with chronic diffuse nephritis or other conditions involving increased arterial tension. They may occur locally in connection with tumors, especially in the uterine fibromyomata. In various acute infections—diphtheria, scarlatina, typhoid fever, influenza, pneumonia, and pyemia—localized lesions of the medium-sized arteries may occur, leading to sclerosis. There is degeneration of the smooth muscle cells and the elastic tissue of the media, occurring in patches and followed by necrosis. These local lesions may heal by connective-tissue formation, or they may involve the intima, leading to sclerosis and more or less obstruction of the lumen. The aorta, the arteries of the brain, and the coronaries are frequently involved.[2]

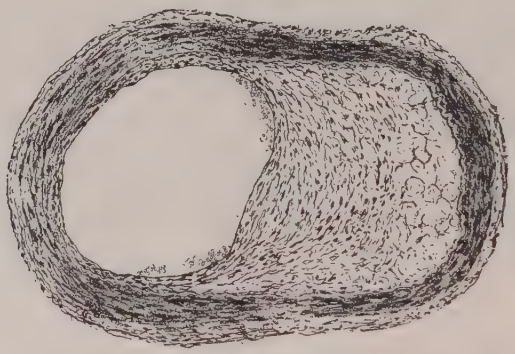


Fig. 392.—Chronic Arteritis—Arteriosclerosis.
Showing pouching of the wall of the artery at the side on which is the largest formation of new fibrous tissue.

While the mechanical conditions under which arteriosclerosis develops are not very fully understood, the primary lesions have been considered by Thoma as a compensatory hyperplasia of the intima. If for any reason—congenital defects, for example—the wall of the artery in a given region, as is the case in the circumscribed or nodular forms of arteriosclerosis, be weakened and yield to the blood pressure, it is at this point that the new tissue forms in the intima and restores the lumen to its natural caliber (see Fig. 385 and 392) with restitution of the rate of blood flow. That this compensation is often incomplete or temporary, or that it brings with it other and often serious complications, does not militate against this view of the significance of these blood-vessel lesions, which are only one of many examples of imperfect adaptation in pathological processes.[3]

[1] For changes in elastic tissue in aorta in advancing age, see *Foster, L. S.*, Jour. Med. Research, 1909, N.S. xv, 297.

[2] See *Wiesel*, Ztschr. f. Heilk., Abt. f. path. Anat., 1906, xxvii, 262.

[3] See *Welch*, Trans. Cong. Am. Phys. and Surg., 1897, iv, 284; and *Faber*, Die Arteriosklerose, Jena, 1912 (bibl.).

Many conditions other than congenital defects in the vessel walls may result in arteriosclerosis. In fact, any long continued disturbance of the normal balance between the blood pressure and the resistance of the vessel wall apparently may lead in a variety of ways to arterial changes. Thus syphilitic inflammation of the arterial wall with necrosis may result in the formation of scar tissue, replacing the muscular and elastic supports of the walls by less resistant structures. The effects of alien substances or of natural substances in undue amount in the blood, which induce a continuing contraction of the muscularis of the arteries, or of overwork may lead through a primary hypertrophy followed by degeneration of the muscle cells to a general weakness of the walls with coincident general or local thickening of the intima. The aortic scleroses produced in rabbits by injections of adrenaline are probably of this class. Senile or other general degeneration of the media with widespread calcareous deposits may determine sclerotic changes in the intima. In all these cases the intimal thickening is not, according to the widely entertained view, inflammatory, but has the nature of a replacement hyperplasia in walls damaged and weakened in various ways.

But this view, largely inspired by the work of Thoma,[1] that the intimal lesions in arteriosclerosis are compensatory, has not found universal acceptance. Indeed there are many conditions under which it seems clear that the sclerotic lesions of the intima, while often associated with damaging or destructive changes in the other layers, especially the media, are not secondary to them but are due to common agents acting on both. Furthermore, there appear to be intimal inflammatory thickenings induced by infective or toxic agents acting primarily on the intima.[2]

The primary fatty changes in the cement substance of the elastic lamina of the vessels have led a number of pathologists to the view that this alteration, with imbibition of plasma leading to further deposits of lipoid substances, may be of fundamental importance in explaining the non-inflammatory types of arteriosclerosis. The breaking-down of the lipoids sets free fatty acid which, by combining with calcium salts, leads to calcification of the tissue. The cholesterin also set free crystallizes and incites connective tissue reactions.[3]

Finally, there may be lesions of the intima secondary to those of the media, without the former being in any sense compensatory.

Classification of the Forms of Arteriosclerosis.—Various classifications of the lesions of arteriosclerosis have been made. These must all be considered somewhat arbitrary and superficial until our knowledge of the mechanics of the circulation and the evolution of the lesions are more clearly defined. Much of the uncertainty in the inter-

[1] See *Thoma, R.*, Virchows Arch., 1883, xciii, 443; 1889, cxvi, 1; Arch. f. Entwickl. Mech., 1901, xii, 352; and Textbook of General Pathology, Eng. trans., vol. i.

[2] For summaries of more recent conceptions of arteriosclerosis, see *Adami, J. G.*, Am. Jour. Med. Sc., 1909, cxxxviii, 485; *Klotz, O.*, Jour. Exper. Med., 1910, xii, 707; and *Frothingham, C.*, Bull. Johns Hopkins Hosp., 1913, xxiv, 323. For production of arteriosclerosis by injection of diphtheria toxin, see *Bailey, C. H.*, Jour. Exper. Med., 1917, xxv, 109; and *Saltykow*, Zieglers Beitr., 1908, xliii, 147. A general bibl. up to 1903 is given by *Thorel*, Lubarsch-Ostertag, Ergebn. d. allg. Pth., 1903, ix[1], 559.

[3] See *Aschoff*, Arteriosklerose, Med. Klin., 1914, x., Beiheft.[1] For experimental production of atheroma by feeding with cholesterol, see *Bailey, C. H.*, Jour. Exper. Med., 1916, xxiii, 69.

pretation of arterial lesions is due to the fact that observations in the past have been made largely on vessels in the contracted condition in which the cessation of blood pressure at death left them, so that the exact condition of the lumen during life in various sclerotic lesions is not really known. Thoma places in one class the primary and more limited nodular forms of fibrous-tissue growth, especially in the larger vessels, which he regards as compensatory in the way just indicated; in another the diffuse or secondary form, which is attributable to an increased resistance to the flow of blood in peripheral vessels, such as those of the kidney, a weakening of the muscularis through degeneration, the consequent dilatation, and then the compensating fibrous-tissue growth in the vessels at large.

Other observers[1] group the lesions into three forms: 1st, the *nodular*, corresponding with the primary form of Thoma; 2d, a *senile* form, in which there are often great distortion of the vessels, calcification, and frequent thinning of the walls; atrophic changes in the viscera are apt to be associated with this form of senile arteritis; 3d, a *diffuse* form of marked obliterating endarteritis with fibrous involvement of the muscular layer. This is apt to be associated with hypertrophy and often with dilatation of the heart, as well as with chronic diffuse nephritis with atrophy. The arterial changes may be marked in the liver as well as in the kidneys.

Periarteritis Nodosa.

A few cases have been described of an acute febrile disease in which many of the small arteries in the muscles and in the viscera were beset with small white knobs projecting from the side or surrounding the vessels. These circumscribed thickenings of the vessel walls are apt to involve all the layers of the vessel, and may encroach upon the lumen. The thickened portions are infiltrated with leucocytes. Multiple aneurysms may develop at the seat of the local thickening.[2] The course of the disease is rarely longer than three months, and it is usually fatal. It is supposed to be of an infectious nature, but this is as yet unproved. In some cases a Wassermann reaction has been obtained, but the Treponema pallidum has not been demonstrated in the lesions.

Tuberculous Arteritis.—Tuberculosis of the arteries is usually secondary, the process extending to their walls from an already established vascular focus.[3] Tubercle tissue with necrosis may involve the external layers, while an obliterating inflammation often closes the lumen. Thus it is that in tuberculous cavities of the lungs large arterial trunks may be laid bare (see Plate XII) without a distribution of the bacilli through the body and without hemorrhage. Tuberculosis of the aorta is of occasional occurrence.[4]

[1] For a résumé of views based upon Thoma's studies, see *Councilman, W. T.*, Tr. Assn. Am. Phys., 1891, vi, 79. For a general study of pathogenesis of arteriosclerosis, see *Pic* and *Bonnamour*, Jour. de phys. et de path. gén., 1906, viii, 495 (bibl.).

[2] Consult *v. Kahlden, C.*, Zieglers Beitr., 1894, xv, 581; *Graf, E.*, ibid., 1896, xix, 181; *Klotz, O.*, Jour Med. Research, 1917, N. S., xxxii, 1; *Dickson, W. E. C.*, Jour. Path. and Bacteriol., 1907, xii, 31 (bibl.); and *Guldner, E.*, Virchows Arch., 1915, ccxix, 366 (bibl.).

[3] For a study of tuberculosis of arteries, see *Geissler*, Virchows Arch., 1906, clxxxvi, 135 (bibl.).

[4] *Haythorn, S.*, Jour. Am. Med. Assn., 1913, lx, 1413; *Woolley*, Bull. Johns Hopkins Hosp., 1911, xxii, 82, and *Blumer, G.*, Am. Jour. Med. Sc., 1899, cxvii, 19 (bibl.).

Syphilitic Arteritis.—A characteristic form of arteritis is due to syphilis, the vessel most frequently affected being the aorta.[1] The lesion in this viscus is confined, as a rule, to a definite portion, especially the ascending and transverse parts, with a fairly sharp line of demarcation between the diseased area and the remainder of the aorta, which may be fairly normal; indeed, the abdominal aorta is almost entirely immune. That portion of the vessel which is diseased is usually dilated and may show aneurysmal pouching. The smooth, glistening, pale yellow appearance of the intima disappears early in the disease and instead there are seen irregular white areas intermingled with dull yellowish patches of fatty degeneration. The mouths of the coronary and intercostal arteries are frequently surrounded by a raised ring of new-formed tissue and the openings reduced to pinpoint size.

Microscopically, the most constant feature of syphilitic aortitis is a round-cell infiltration of the outer coats of the vasa vasorum, the infiltrating cells being of the lymphocytic or plasma-cell type. Giant cells are, as a rule, very few but occasionally are abundant in small gummatous areas. They should be distinguished from the foreign body type often found inclosing elastic fibers or cholesterin crystals. In addition to the small-cell infiltration there is a fibrous thickening chiefly in the adventitia and only occasionally is there much degeneration in the media or intima. The elastic fibers are fragmented and granular and often much reduced in number. Ultimately the lumen of the smaller vessels is greatly reduced or entirely obliterated by the new-formed tissue. In the late stages small areas of cellular fibrous tissue sometimes inclosing necrotic zones may be found in the media. About these areas there is often, in addition, a lymphocytic infiltration.

While a positive Wassermann reaction is present in all but about 5 per cent. of persons suffering from aortitis, the demonstration of the Treponema pallidum is rarely possible.[2]

The aortic valves are involved in about half the cases. Cardiac hypertrophy is not often found in connection with syphilitic aortitis, even though regurgitation exists. The coexistence of aneurysm is not very frequent, certainly in not more than 30 per cent. of the cases and in some series not more than 20 per cent. It is more frequent in males than in females. Some degree of aortitis is usually present in all untreated syphilitic patients, even in children, and is occasionally seen also in tabetic and paretic persons.[3]

In addition to the aorta, other vessels of the body may suffer syphilitic changes, which are especially noteworthy in the brain and spinal cord. The alterations in these regions may be very early, even congenital, and

[1] *Chiari*, Verhandl. d. deutsch. path. Gesellsch., 1904, vi, 137; *Benda*, ibid., 164; *Marchand*, ibid., 197; *Gruber*, Uber die Doehle-Heller'sche Aortitis (Aortitis luetica), Jena, 1914; *Thorel*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1911, xiv[2], 681; *Larkin, J. H.*, and *Levy, I. J.*, Jour. Exper. Med., 1916, xxiii, 1; *Symmers, D.*, and *Wallace, G. H.*, Jour. Am. Med. Assn., 1916, lxvi, 397; *Moore, W. C.*, Am. Jour. Med. Sc., 1918, clv, 660.

[2] For demonstration of Treponema pallidum in five cases of syphilitic aortitis, see *Wright, J. H.*, and *Richardson, O.*, Boston Med. and Surg. Jour., 1909, clx, 539.

[3] For a clinical study of the disease, see *Longcope, W. T.*, Arch. Int. Med., 1913, xi, 15, *Schrumpf, P.*, Arch. f. Dermat. u. Syph., 1918–19, cxxvi, 793.

may precede the occurrence of symptoms, as shown by the characteristic changes in the spinal fluid, the presence of globulin, a high lymphocyte cell count, and changes in the colloidal relationships of the salts and proteins demonstrated by the colloidal gold test.[1]

While, as has been stated, vascular disease is occasionally found in tabes and paresis, there may be very extensive cerebral vascular syphilis without degenerative changes. In other words, a certain number of cases of cerebral hemorrhage and softening are due to specific mesarteritis.[2]

ESSENTIAL HYPERTENSION.

While the elevation of the blood pressure above the normal is usually due to chronic disease of the kidney, there is a type known as essential hypertension, in which the kidney is not sufficiently diseased to warrant the assumption that it is responsible for the increased blood pressure. The constant lesion found is a mural disease of the terminal arterioles. In practically all cases the terminal arterioles in the kidney are affected, those of the spleen in about 60 per cent. of the patients; those of the pancreas in about half; those of the liver about a third, and the brain about a fifth. On the other hand, the terminal arterioles of the skin, skeletal muscles, myocardium, and those of the lungs and gastrointestinal tract, are very rarely involved, and then to a very insignificant extent. Thus the distribution of this lesion of the arterioles is different from that of the large vessel arteriosclerosis, for the latter is seen chiefly in the vessels of the heart, brain and extremities. The lesions in the kidney are in typical cases very slight indeed. After a glomerulus becomes hyalinized as a result of a sclerotic process in its vas efferens, the corresponding tubules also atrophy. Such kidneys exhibit only foci of arteriosclerotic scarring, and between such scarred areas ample parenchyma remains to sustain the excretory functions of the organ.[3] Moschcowitz hold that it is probable that the hypertension is responsible for some of the arterial lesions and that it ultimately induces an anatomic nephritis. Others think it an expression of a hypercholesteremia followed ultimately by a series of vascular and even renal changes.

ANEURYSM.

An aneurysm is a dilatation of an artery and may be either cylindrical, fusiform, or sacculated. Initially, when the protuberance is small, the walls consist of all coats; later, rupture of the elastic and other layers takes place; and the wall of an aneurysm of any considerable size is formed by connective tissue of a cicatricial type, probably originating in the adventitia and the structures immediately external to that coat. Often there is a thick laminated layer of fibrin lining the sac in addition

[1] *See Black, Rosenberg,* and *McBride,* Jour. Am. Med. Assn., 1917, lxix, 1855. For a simple procedure for the preparation of colloidal gold for diagnostic purposes, see *Lee, O. I.,* Am. Jour. Med. Sc., 1918, clv, 404.

[2] For discussion of some problems in the pathology of syphilis, see *Fordyce, J. A.,* Am. Jour. Med. Sc., 1915, cxlix, 781.

[3] *Fishberg, A. M.,* Arch. Int. Med., 1925, xxxv 650; *Moschcowitz, E.,* Problems in Renal Pathology, Am. Jour. Med. Sci., 1926, clxxii, 469.

to the external so-called vascular callus[1] composed of dense connective and new-formed elastic tissue.

The aneurysmal sac is usually lined with endothelium; this is not the result of a mere stretching of the normal covering of the inner surface of the vessel, but is due to an ingrowth of cells from the borders of the rupture. Thus the older view, that the sac of an arterial aneurysm is solely the result of the dilatation of a vascular wall, must be abandoned.

The conditions which commonly lead to aneurysms are arteriosclerosis, either with or without associated degeneration; such local

Fig. 393.—Fusiform Aneurysm of the Arch of the Aorta.

weakening of the walls of the vessels, from various causes, as often leads to compensatory arteriosclerosis, but in which protective compensation does not take place; or the blocking of a vessel by embolus or trauma. Syphilis is probably the most important single factor, being demonstrable in 20 to 30 per cent. of the cases. Aneurysms may develop at the point of partial rupture of the walls of an artery. They may follow the local necrotic and ulcerative process in the walls of the vessels or on the heart valves incited by infectious agents, which as emboli or otherwise have reached these parts. Such mycotic aneurysms are frequently multiple.[2]

[1] *Manz*, Zieglers Beitr., 1898, xxiv, 531.

[2] For a study of mycotic aneurysms, with bibl., see *McCrae, J.*, Jour. Path. and Bacteriol., 1905, x, 373.

In **cylindrical or fusiform aneurysm** there is apt to be at first a distention of all the walls of the vessel; but this is often irregular, so that the sac may bulge more in one place than in another (Fig. 393). The walls may become thin or through new-formed tissue may become thickened; they may undergo degeneration or calcification. Such aneurysms are most frequent in the aorta, but may occur in other vessels.

In the **sacculated aneurysm** there is either a dilatation of the entire circumference of an artery over a short portion of its length, or a dilatation of only a small portion of one side of the wall, so that the aneurysm looks like a swelling attached to one side of the artery. The aneurysm may commence as a dilatation of all the coats of the vessel; but the middle coat may soon atrophy, so that the wall is composed of the inner and outer coats; or the inner coat may be destroyed by endarteritis, so that

Fig. 394.—Aneurysm of the Popliteal Artery.
Showing lamellated clot.

the outer coat alone forms the wall of the aneurysm, all coats finally disappearing; or the dilatation may commence at the seat of rupture of one or more coats of the vessels. As the aneurysm increases in size it may press upon and lead to partial destruction of neighboring tissues and viscera, so that portions of these tissues and viscera may take the place of the wall of the aneurysm. The cavity of the aneurysm is filled with fluid or clotted blood, or with layers of fibrin (Fig. 394) which adhere closely to its wall. The communication between the aneurysm and the artery may be small or large. If arterial branches are given off from the aneurysm they may remain open or become plugged with fibrin; or their walls may be thickened and their cavities narrowed by endarteritis.

Death may occur from the pressure of the aneurysm and interference with the adjoining viscera or by rupture.

Dissecting aneurysms are those in which, owing to a solution of continuity of the inner layers of the artery, the blood gets between the media and adventitia, and forces its way for a greater or less distance between them, or separates the media into two layers.[1]

Spurious or false aneurysms are most frequently connected with vessels of the extremities. When an artery is wounded the blood escapes into the surrounding soft parts, and a cavity is formed filled with blood and broken-down tissue.

The wound in the artery may heal and the effused blood be absorbed; or it may become the seat of secondary inflammatory processes.

Finally, a wall of fibrous tissue may be formed, while the wound of the artery remains open, so that there is an aneurysmal sac through which the blood is constantly pouring. This is called a *false aneurysm.* It does not, however, differ from a true aneurysm after the latter has reached a certain size.

Aneurysmal Varix: Varicose Aneurysm.—If an artery be wounded, and at the same time the vein which accompanies it, we have as the result the conditions called *aneurysmal varix* and *varicose aneurysm.* In aneurysmal varix the artery and vein become adherent at the seat of injury, so that the arterial blood passes directly into the vein. There is a smooth, rounded opening between the two vessels, the vein is dilated into a sac, and the veins emptying into it are dilated and tortuous. In varicose aneurysm the artery and vein do not communicate directly, but a false aneurysmal sac is formed between the vessels, into which the blood is poured before passing into the vein. Varicose aneurysm may also be formed by the spontaneous rupture of an aneurysm into a vein. The aneurysm presses against the vein, becomes adherent, and finally ruptures into it. This condition has been observed between the aorta and pulmonary artery; the aorta and inferior and superior vena cava; the popliteal artery and vein; the femoral artery and vein; the splenic artery and vena azygos; the internal carotid and sinus cavernosus.

Cirsoid aneurysm is one formed by the dilatation and lengthening of large or small arteries or arterial tracts. The walls of the arteries are thinned, the vessels are tortuous and in places sacculated. These changes are most frequent in small arteries, especially the temporal and occipital. They involve the trunk of the vessel and its branches, or may extend to the capillaries and small veins. They form larger or smaller tumors beneath the skin.

ANEURYSMS OF THE DIFFERENT ARTERIES.

The aorta may be dilated over its entire length, or there may be diffuse or circumscribed dilatations at any portion of its course; or there may be several aneurysms, situated at different points. The ascending portion of the arch of the aorta may be uniformly dilated in a fusiform shape

[1] For a study of dissecting aneurysm, see *Adami*, Montreal Med. Jour., 1896, xxiv, 87, 410.

(Fig. 394), or there may be circumscribed dilatations on its anterior wall, or, more rarely, on its posterior wall. The sacculated aneurysms vary in size and may rupture within the pericardium; or they may form a cavity in the upper part of the ventricular septum and communicate by openings into the pulmonary artery and left ventricle; or they may dilate downward between the visceral and parietal pericardium, in front of the heart, pushing that organ backward. They may perforate into the right or left auricle or right ventricle, the superior vena cava, or the pulmonary artery; or they may reach a large size, press on and erode the right side of the sternum and adjoining ribs, project under the skin, and even rupture externally.[1]

The transverse portion of the arch may be dilated in a fusiform shape, or there may be sacculated aneurysms at any point in its wall. The sacculated aneurysms usually reach a considerable size. They press on the sternum and ribs in front, or on the esophagus, trachea, and bronchi behind. The large arteries given off from the arch may be occluded. They cause death by pressure on the air passages, the esophagus, and the vena cava; or may rupture externally or into the esophagus, trachea, bronchi, pulmonary artery, or pleural cavities.

On the abdominal aorta aneurysms are usually sacculated. If they are situated high up they may project into the pleural cavities; if lower down, into the abdomen. They may compress and displace the viscera, vessels, and nerves, and erode the vertebræ. They may rupture behind the peritoneum, into the peritoneal cavity, the pleural cavities, the inferior vena cava, the bronchi, the lungs, the duodenum, the colon, the pelvis of the kidney, or the posterior mediastinum. Rupture of the aorta with the development of a long dissecting aneurysm parallel to the vessel may give rise to a condition simulating a double aorta.[2]

The coronary arteries may be dilated throughout, or may be the seat of small sacculated aneurysms.[3] These may rupture into the pericardium, or may lead to rupture of the heart wall.

The pulmonary arteries are rarely the seat of aneurysms. Diffuse and circumscribed dilatations, however, sometimes occur on the main trunk and on the two principal branches of the artery. They do not usually reach a large size, but may cause death by rupture. General dilatation of all the branches of the pulmonary artery is more common. It is found in connection with stenosis of the mitral valves and with compression or induration of the lung tissue. Small multiple aneurysms—*miliary aneurysms*—may occur in the cerebral arteries; less frequently in the pulmonary and mesenteric. These are probably due to some congenital weakness of the walls at the point of formation of the aneurysm.

Of the other arteries of the body there is hardly any one which may not become the seat of an aneurysm.[4]

[1] For extension of aortic aneurysm into the heart, and dissecting aneurysms of the heart, see *Hektoen, L.*, Trans. Assn. Am. Phys., 1901, xvi, 127.

[2] See case reported by *G. P. Biggs*, Proc. New York Path. Soc., 1897–98, p. 109.

[3] Consult *Capps, J.*, Am. Jour. Med. Sci., 1899, cxviii, 312 (bibl.); also *Griffith*, Brit. Med. Jour., 1901, i, 266 (bibl.).

[4] For details concerning form, distribution, and frequency of aneurysms see the larger works on the practice of medicine or surgery.

STENOSIS AND OBLITERATION OF THE AORTA.

This lesion near the entrance of the ductus arteriosus has been observed in a considerable number of cases. The degree of stenosis varies. The aorta may be entirely closed and converted into a solid cord for a half-inch; or there may be a constriction through which there is a larger or smaller opening. The walls of the aorta at this point may be thickened and sclerosed. The ductus arteriosus may be closed or open. Above the constriction the aorta is usually dilated; below it, it is normal, dilated, or stenosed.

Stenosis of the aorta is followed by hypertrophy of the left ventricle, and, later, of the right ventricle, with venous congestion throughout the body; or there may be a collateral circulation developed between the arteries given off above and below the constriction; or there may be rupture of the aorta, or of the right ventricle or auricle.

This condition is found at all ages, but is induced during fetal life or in the first year of extrauterine life. It is probable that it may be caused after birth by an abnormal closure of the ductus arteriosus. This vessel normally becomes closed without the formation of a thrombus. If a thrombus is formed it may extend into the aorta and obstruct it; or the ductus arteriosus may be filled with a thrombus, but for a time increase in size; afterward, as the thrombus is absorbed, the vessel may contract and draw the walls of the aorta together.

TUMORS.

For a description of **angioma,**[1] see page 432.

Primary malignant new growths of the arteries are so rare as to be almost unknown; a few **sarcomata** of the aorta, however, are said to have been reported.[2]

Secondary growths, chiefly **carcinoma** and **sarcoma,** may occur in the walls of the arteries by continuous growth from without, involving first the external layers. To these they are usually confined, for the density of the inner coats offers such distinct resistance to infiltration by the tumor cells that arteries may, and often do, pass intact through tumors encircling them.

Arteries become secondarily involved by malignant neoplasms more often through the deposition of tumor-cell emboli. These are usually of small size and are apt to get into the circulation by growing through the walls of the veins into their lumina; large ones most frequently lodge in the branches of the pulmonary artery. Composed as they are for the most part of cells capable of proliferation, tumor emboli are apt soon to form connection with the wall of the vessel, and by the growth into them of blood-vessels from the vasa vasorum to find the conditions necessary for their development, so that they may soon involve the entire wall and even grow out into adjacent parts.

But not all emboli which attain the circulation are able to obtain a

[1] Bibl. by *Thorel*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907, xi[2], 194.
[2] *Benda*, Aschoff, Pathologische Anatomie, Jena, 1913, ii, 87.

foothold,[1] those from tumors of slow growth perishing before they have time to effect a union with the endothelium and become vascularized.[2]

The Veins.

DILATATION. (Phlebectasia, Venous Varicosity.)

Dilatation of the veins, or phlebectasia, occurs under a variety of forms:

1. Simple Dilatation.—The vein is uniformly dilated in a cylindrical or fusiform shape; its length is not increased; its walls may be thicker than normal or thinned; the valves are thickened, or are insufficient, or atrophic, or are torn.

2. Cirsoid Dilatation.—The vein is cylindrically dilated, but is also increased in length, so that it assumes a very tortuous course. The walls may be thickened or thinned.

3. Varicose Dilatation.—Portions of the wall of the vein undergo saccular dilatation. The wall of the sac is formed of the coats of the vein, but these may be thickened or thinned; the middle coat may disappear entirely. There may be only one such dilatation, or there may be a number on the same vein, or a number of veins may be affected at the same time. The vein may be otherwise normal, or, more frequently, may be more or less uniformly dilated.

4. Anastomosing Dilatation.—A number of contiguous and anastomosing veins are dilated, both in the cirsoid and varicose forms. The vein then looks like a series of cavities separated by thin partitions. The dilatations of the same vein become adherent to each other and to those of the adjoining veins; portions of the walls of the dilated parts may atrophy so that there may be a number of cavities containing venous blood and separated from each other by thin partitions.

Distribution, Causes, and Effects of Phlebectasia.—There is hardly one of all the veins of the body which may not be dilated. The hemorrhoidal veins, forming "hemorrhoids;" the veins of the leg and thigh; those of the pelvis and pelvic viscera; those of the spermatic cord, scrotum, and labia; those of the abdominal wall; those of the neck and arms—are most frequently involved. The immediate cause of dilatation is usually some obstruction to the passage of the blood through the veins toward the heart as in the esophageal varicosities, the caput medusæ of hepatic cirrhosis, or the varices of the lower extremity which occur with great frequency in women following repeated pregnancies. Alterations in the walls of the vessels from degeneration, inflammation, or injury must often be important predisposing factors, however, for purely mechanical conditions cannot account for all of the phenomena observed. For example, the older idea that varices are due to leakage from the valves of the veins in the legs is negatived by the fact that the greatest dilatation is on the peripheral side of the valve, not central, as it would be if pressure played a large part. The lesions found are very variable. Sclerotic and

[1] *Schmidt*, Der Verbreitungswege der Karzinome, Jena, 1903.
[2] *Takahashi*, Jour. Path. and Bacteriol., 1915, xx, 1.

fibrous changes in the walls with atrophy of the muscle, rupture of the elastic laminæ, and small-cell infiltration of the perivascular connective tissue are seen. In all probability, the inflammation occurs chiefly in those veins in which the pressure is high, and the progress of the disease amplifies the initial lesion set up by mechanical factors. Spontaneous restitution of dilatations of the veins is not common, and usually occurs only in the lesser degrees of the lesion. The tendency of the dilatation is to increase. Thrombi frequently form in the dilated veins, and either partially or completely fill them. These thrombi may become organized, or they may dry and become calcified, forming *phleboliths*. These have received much attention of late, for they have frequently been taken for calculi in the ureter and, on the basis of an uncontrolled *x*-ray plate, have led to a considerable amount of meddlesome surgery. By the formation of new connective tissue in the walls, the thrombi may become inclosed in a fibrous capsule and permeated by capillaries, with the ultimate obliteration of the vessel by connective tissue. The wall of the dilated sac may become so thin that it finally ruptures. Inflammation of the dilated vein may occur, and be followed by fibrous thickening. When occurring in mucous membranes, dilated veins are usually associated with persistent catarrh.

WOUNDS—RUPTURE.

Wounds of the veins usually heal by a simple contraction and an adhesive inflammation of their walls; sometimes by the formation of a thrombus. **Rupture** of the veins may be produced by severe contusions and crushings of the body and by violent falls. **Perforation** of a vein may be produced by suppuration of the soft parts and the invasion of the walls of the vessel; by the pressure of an aneurysm or of a new growth; or by the thinning of the wall of the vein in phlebectasia.

THROMBOSIS.

Thrombosis of the *inferior vena cava* has been many times recorded. It is usually due to pressure on the vessel or may occur as an extension of thrombi from the contributory veins.[1]

Thrombosis of the *superior vena cava* usually follows pressure from without by tumors, aneurysms, or enlarged lymph-nodes.

Thrombosis of other *large venous trunks* may occur under various local and general conditions (see below, Phlebitis, and page 35).[2]

DEGENERATION.

Fatty degeneration and **calcification** may occur in the walls of the veins under conditions similar to those in which these changes take place in the arteries.

[1] For a case of complete fibrous obstruction of superior and inferior venæ cavæ, see *Meyer*, Mt. Sinai Hosp. Rep., 1903, iii, 35.

[2] For a consideration of peripheral venous thrombosis in heart disease, consult *Welch, W. H.*, Trans. Assn. Am. Phys., 1900, xv, 441 (bibl.).

INFLAMMATION. (Phlebitis.)

Inflammation of the veins, *phlebitis*, may involve chiefly the external layers—*periphlebitis;* or the internal—*endophlebitis;* or, as is very frequently the case, the entire wall may be affected. Phlebitis may be due to an infectious thrombus, to injuries, or to an infectious inflammation of the surrounding tissues. Thrombosis of the vein, either primary or secondary, is a very constant accompaniment of phlebitis. Thrombosis and phlebitis are not infrequent in association with or following infectious diseases, especially endocarditis, in cachectic conditions, and in rheumatism and gout.

Acute infective phlebitis may follow a suppurative periphlebitis. The outer layers of the vein wall are congested, swollen, infiltrated with serum and pus. The inner coats may become infiltrated with pus; they may become necrotic and disintegrate. A thrombus is constantly formed under these conditions, which may for a time stop the circulation and keep the products of inflammation and degeneration and infectious

FIG. 395.—TUBERCULOUS PHLEBITIS.
The section is from one of the pulmonary veins in a child dead of acute general miliary tuberculosis.

material from mixing with the blood; but the thrombus itself is prone to disintegration, and thus the exudates and fragments of disintegrated thrombi or tissue or bacteria may enter the circulation.

On the other hand, owing to the presence of irritating or infectious material within the vein, and the formation of a thrombus, the inflammatory process may be at the commencement an endophlebitis, but usually, if the inflammation be at all severe, the entire wall of the vessel is eventually involved.

Acute phlebitis may terminate in the absorption of the thrombus and the return of the vein to its normal condition, or in the obliteration of the vein. The pyogenic cocci, the typhoid bacillus, the pneumococcus, and several other microorganisms have been found in phlebitis. In the phlebitis with thrombosis which frequently complicates infectious diseases such as typhoid fever, pneumonia, etc., the bacteria present are often not those which are the excitants of the primary disease.

The most important results of phlebitis are usually those which depend

upon the introduction into the blood of infectious or other emboli (page 39). The relationship between non-infectious thrombi and phlebitis is in many cases not clear.[1]

Chronic periphlebitis results in thickening, principally of the outer coats of the veins, but the inner coats also may be involved. The surrounding tissue may also be thickened and coalesce with the walls of the vein. There may or may not be thrombosis.

Chronic endophlebitis is a not very common lesion, of the same general character as chronic endarteritis, with which it is often associated. More or less circumscribed patches of new connective tissue are formed in the inner coats, which may undergo fatty or calcareous degeneration.

Tuberculous inflammation of the walls of the veins may occur as an extension of the process from without or from a lodgment of the tubercle bacilli in the blood current on the intima (Fig. 395). This is most frequent in the pulmonary veins, and Weigert has called attention to the fact that in acute miliary tuberculosis the growth of tubercle tissue into the lumina of these veins from tuberculous lymph-nodes is of frequent occurrence and readily explains the topography and mode of occurrence of the general disease. The tubercle bacilli which are present in the tuberculous tissue growing into the lumen of the veins find thus an easy distribution.[2]

Syphilitic inflammation may involve the walls of the veins either as gummata or as more diffuse thickenings; even complete obliteration may occur.

TUMORS.[3]

For a description of **angioma,** see page 432.

Other benign tumors of the veins include **leiomyoma** and **fibroleiomyoma.**[4] Myoma of the uterus is regarded by some observers as perhaps derived from the walls of the uterine blood-vessels,[5] rather than from the uterus itself.

Sarcoma of the veins has been recorded.[6]

PARASITES.

Echinococcus is sometimes found in the veins, having either developed there or perforated from without.

Several species of **trematodes** are found in the circulation in man. *Fasciola hepatica* (*liver fluke*) occurs rarely and, while usually found in the bile-ducts, may be present in the vena cava. *Schistosoma hæmatobium* is very common in man in Egypt and in other parts of Africa, and usually occurs in the portal vein or its branches, and frequently in other veins.

[1] Consult in this connection *Welch* on Thrombosis, Allbutt, System of Medicine, 1909, vi, 170.

[2] See *Ribbert*, Deutsch. Med. Wchnschr., 1906, xxxii, 5.

[3] Bibl. by *Schnyder*, Centralbl. f. allg. Path., 1914, xxv, 529; *Thorel*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix[1], 559; 1907, xi[2], 194.

[4] *Ecoffey*, Arch. de méd. expér., 1917, xxvii, 454.

[5] *e.g., Knauer*, Festschr. f. Chrobak, Vienna, 1903, i, 695 (bibl.); *Borst*, Die Lehre von den Geschwülsten, Wiesbaden, 1902, i, 212.

[6] *Pollack*, Berl. klin. Wchnschr., 1904, xli, 1055.

The Capillaries.

The walls of the capillaries are so thin and so intimately connected with the surrounding tissues that their lesions are studied most appropriately among the diseases of the several organs. Dilatation of the new-formed capillaries in tumors, granulation tissue, etc., fatty, amyloid, and hyaline degeneration of their walls, and capillary aneurysms, may be mentioned here as readily observed lesions occurring under a variety of conditions. Angiomas and telangiectases, usually congenital, are occasionally seen.

The changes which we assume to occur in the walls of the smaller veins and capillaries in exudative inflammation, by reason of which fluids and blood cells pass through them, are not yet sufficiently understood to be described with definiteness.

The Lymph-Vessels.

General Characters of the Lymph-Vessels.

The larger lymph-vessels are often the seat of various more or less abundant lesions. They form, with their many ramifications into the tissues, a closed system, though a large number of the smaller vessels can hardly be demonstrated except by ink injections, because their walls are so closely bound with the tissue through which they pass. It is now held that there is no direct communication between the tissue spaces, which lie between the individual cells, and the lymph-capillaries, and that all interchange of fluid takes place through a distinct wall of endothelial cells.[1] As has been stated elsewhere, the ultimate drainage of the lymph-vessels is through the lymph-nodes, which act as filters for inert particles and bacteria and probably to a certain extent as absorbing tissues which receive the brunt of the toxic action of certain bacterial and other poisons derived from foci in the tissues.

LYMPHANGIECTASIS.

Dilatation of the lymph-vessels occurs under a variety of conditions. It may be congenital, or it may be due to some hindrance to the flow of lymph onward—as by pressure from any cause, or from the occlusion of the vessels by inflammation. If the dilated vessels form a circumscribed mass, this is often called a **lymphangioma** (Fig. 229). In certain forms of *elephantiasis* and in *macroglossia* the dilatation of the lymph-vessels is an important factor. Its occurrence is not infrequent in the labia, prepuce, and scrotum. Dilatation of the chyle vessels may occur in the mucous membrane of the intestine and in the mesentery. Filarial lymphatic varix is of occasional occurrence.[2]

Obstruction of the thoracic duct may be due to tumors,[3] or enlarged lymph-nodes, or inflammatory processes in the mediastinum; to aneurysm, to thrombosis of the left innominate vein, to insufficiency of the tricuspid valve; or to inflammatory processes in the wall of the duct. It may occur under various other conditions. It may be compensated by

[1] *Adler* and *Meltzer*, Jour. Exper. Med., 1896, i, 482.

[2] See *Opie*, Filarial Lymphatic Varix, Trans. Assn. Am. Phys., 1901, xvi, 331.

[3] For bibliography of carcinoma involving the thoracic duct, see *A. H. Smith*, Med. Record, 1899, lvi, 813.

collateral lymphatic anastomoses, or it may lead to various lymph-angiectasiæ and to transudation of lymph. Thus chylous ascites may occur.

Congenital doubling or division and other abnormalities of the thoracic duct are recorded.[1]

LYMPHORRHAGIA.

If through injury, necrosis, or other pathological process, the walls of the lymph-channels suffer solution of continuity the lymph may escape into surrounding tissues or spaces. Thus, upon the surface of the skin or into loose connective-tissue spaces or into the great body cavities, lymph may be poured out. A chylous hydrothorax or chylous ascites may occur from a rupture of the thoracic duct or its radicles. Chyluria may result from a similar injury to the lymphatics in the bladder or ureter.

THROMBOSIS.

Thrombi may form in the lymph-vessels by the coagulation of the lymph or by the deposition of fibrin on the walls of the vessels at the seat of degeneration or inflammation. These lymph thrombi are formed largely of fibrin and leucocytes. Such thrombi may cause disturbances of the lymph circulation or portions of them may become detached, forming emboli.[2]

INFLAMMATION. (Lymphangitis.)

Acute Infective Lymphangitis.—Inflammation of the larger lymph-vessels is usually secondary and often connected with an infected wound or injury. Owing to the entrance into the lymph-trunk of bacteria or other infectious agents, poison of venomous reptiles, insects, etc., the vessels, sometimes for a considerable distance away from the wound, become red, tender, and painful. Under these conditions the appearances which the vessels present vary. In some cases, the redness disappears after death and we find no appreciable alteration. In other cases, the walls of the lymph-vessels are more or less densely infiltrated with pus cells, there is proliferation of the endothelium, and the lumen may contain variable quantities of pus and fibrin and desquamated degenerated endothelium. The vessel may be occluded by a thrombus. The tissue about the vessels may also be infiltrated with serum and pus. These lesions may undergo resolution and the vessel be restored to its normal condition; or the vessel wall and surrounding tissue may die or become involved in abscess; or new connective tissue may form in and about the vessel, sometimes with obliteration of its lumen. The associated lymph-nodes may participate in the inflammatory process.

Tuberculous Lymphangitis.—Tuberculous inflammation occurs in both large and small lymph-vessels. Miliary tubercles and diffuse tubercle tissue may form in the walls and project into the lumen of the larger trunks; or in the smaller vessels the new growth may entirely fill the

[1] *Butler*, Jour. Med. Research, 1903, N. S. v, 153 (bibl.).
[2] *Opie*, Jour. Med. Research, 1913, N. S. xxiv, 131.

lumen, and grow within it, with more or less involvement of the walls. This may occur independently, but it is most frequently seen in connection with tuberculous inflammation of adjacent tissues. Thus from tuberculous lymph-nodes in the vicinity of the thoracic duct there may be a direct extension of the tuberculous inflammation, an involvement of the walls of the duct, and a growth of tubercle tissue into its lumen. Such growths in the thoracic duct have been shown by Weigert to occur in acute general miliary tuberculosis (page 289). In the vicinity of tuberculous ulcers in the intestines, furthermore, we often see the subserous lymph-vessels, which pass from the vicinity of the ulcers, distended with the products of tuberculous inflammation and looking like dense white knobbed cords (Fig. 487, page 777).

Syphilitic lymphangitis not infrequently occurs in the vicinity of syphilitic ulcers in the primary stage. In later stages there may be thickening of the walls of the vessels and the development of gummata in and about them.

TUMORS.

The primary tumors of the lymph-vessels, the lymphangiomata, are described in the Chapter on Tumors.

The dissemination of malignant tumors through the lymph-channels is of frequent occurrence, and is particularly marked in the case of carcinoma. In the vicinity of carcinomata, the lymph-vessels are not infrequently crowded with the tumor cells, forming white, irregular cords; or small masses of the tumor cells are found in the lymph-vessels, either near to or remote from the tumor. White, irregular networks are often formed in this way beneath the pleura in carcinoma of the lung, or beneath the capsule of the liver. Transverse sections of lymph-vessels thus distended sometimes show swelling and detachment of the endothelium and a crowding of the lumen with tumor cells.[1]

[1] *Unger*, Virchows Arch., 1896, cxlv, 581.

CHAPTER VI.

THE RESPIRATORY SYSTEM.

The Nose and its Associated Cavities.

The nasal cavity is lined for a short distance from its opening with skin covered with flat epithelium, thickly sown with sebaceous glands and containing the hair follicles of the short bristles which project into the lumen. The remainder of the cavity is lined with a mucous membrane which is covered with a layer of ciliated epithelium. The submucosa is composed of a loose connective tissue with some elastic fibers and variable amounts of lymphoid tissue. Mucous glands and a very rich venous complex are also present. The accessory cavities of the nose are lined with a similar but somewhat thinner membrane.

The direction of vibration of the cilia is such that the dust from the air which impinges upon the mucous membrane is swept toward the nares. Owing to its exposed position the membrane is subjected to the action of deleterious agents, and sudden changes of temperature may lead to great and abrupt alterations in the condition of the blood-vessels, and hence, also, to variations in the turgidity of the membrane. Because of its great vascularity and extensive nerve supply, the mucous membrane is very responsive to bacterial infections, to chemical irritation, and to anaphylactic poisoning, the best instances of the last being sensitiveness to the effluvia from horses, which is seen in some individuals, and to plant pollen, which is observable in those suffering from hay fever.

MALFORMATIONS.

Absence or deformity of the nose or some of its parts, deviations of the septum, clefts, usually associated with cleft palate and harelip (Fig. 185 and 186), are among the more frequent of the congenital anomalies of the nose.

HEMORRHAGE. (Epistaxis.)

This may result from injury; it may be an expression of local or general hyperemia from cardiac or vascular lesions, obstruction of vessels, etc. It not infrequently occurs in an early stage of acute infections, such as typhoid fever. It may accompany general conditions such as hemophilia, pernicious anemia, etc. Epistaxis may result from lesions of the nasal mucous membranes, ulcers, telangiectasis, etc.

INFLAMMATION. (Rhinitis.)

Acute catarrhal inflammation is common and often associated with a similar process in the pharynx and larynx. There is at first a hyperemic swelling followed by an increased production of mucus and transudation of serum from the blood-vessels; emigration of leucocytes and desquamation of epithelium may follow. This and other inflammatory processes

may extend to the frontal or ethmoidal sinuses and the antrum, where the exudates may collect (Fig. 396). As the process resolves, the exudation ceases, the epithelium regenerates, and the mucosa is restored to its normal condition.[1]

Pseudomembranous inflammation, either simple or diphtheritic, may involve the nasal cavities. Phlegmonous inflammation involving adjacent parts is of occasional occurrence. Bacteria apparently play an important part as excitants of acute catarrhal and pseudomembranous inflammation.[2]

Chronic catarrhal inflammation may follow the acute form, and is marked by hyperplasia of the fibrous tissue in the submucosa, often followed by atrophy of the mucosa. Ulceration of the mucosa may occur; the exudate may assume a fetid character. A hyperplasia of the mucosa may lead to the formation of the so-called mucous polyps[3] (Fig. 397 and 398). These are usually pedunculated, soft prolapses of the mucous membrane covering a gelatinous and edematous or spongy connective tissue. The palisade cells covering the surface are often ciliated. The vessels are abundant, but have very thin capillary walls. In the interstices of the connective tissue are often collected many eosinophile leucocytes and numerous plasma cells. Hyperplastic mucous glands are occasionally found in the polyps.

FIG. 396.—CATARRHAL INFLAMMATION OF THE MUCOUS MEMBRANE OF THE ANTRUM.

Showing migration of leucocytes through the epithelium.

Tuberculous and syphilitic inflammation with the usual morphological characters of these processes are common in the nasal cavities.

TUMORS.

Aside from the **nasal polyp** (page 455) which may be adenomatous in character, the most common tumors are **sarcoma**[4] and **carcinoma**;[5] both are unusual, but the former is perhaps a little less rare. Carcinoma may be either of the cylindrical-cell, the squamous-cell, or the adenomatous type.[6]

Melanosarcoma[7] and **dermoid cysts** have been described.

[1] For a study of the pollen of plants as excitants of hay fever, see *Liefmann*, Ztschr. f. Hyg., 1904, xlvii, 153, and for résumé of treatment with Dunbar serum, see *Glegg*, Jour. Hyg., 1904, iv, 369.

[2] For a study of the bacteriology of nasal inflammation, see *Howard* and *Ingersoll*, Am. Jour. Med. Sc., 1898, cxv, 520. See also for bacteria of the nose, *Neumann, R. O.*, Ztschr. f. Hyg., 1902, xl, 33; also *Hasslauer*, Centralbl. f. Bakteriol., Ref. I, 1906, xxxvii, 1 (bibl.). For a study of the lymph-vessels of the nose and pharynx, see *Most, A.*, Arch. f. Anat. u. Physiol., Anat. Abth., 1901, i, 75, 94.

[3] For a summary of facts concerning the nature of the ordinary nasal polyps, see *Wright*, Med. Record, 1901, lix, 132 (bibl.).

[4] *Sonnenschein*, Arch. f. Laryngol. u. Rhinol., 1909, xxii, 528 (bibl.).

[5] *Trautmann*, Arch. f. Laryngol. u. Rhinol., 1905, xvii, 386 (bibl.).

[6] *Cordes*, Berl. klin. Wchnschr., 1903, xi, 164 (bibl.).

[7] *Cozzolino*, Arch. f. Laryngol. u. Rhinol., 1903–04, xv, 77.

FIG. 397.—MUCOUS POLYP OF THE NOSE.

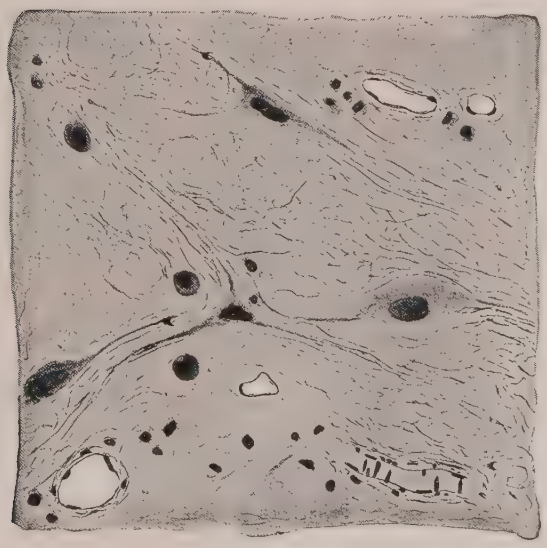


FIG. 398.—MUCOUS POLYP OF THE NOSE.
Showing branching cells with loose delicate stroma containing much fluid.

Benign tumors of the nasal septum have been recorded.[1]

Adenoids.—In many children there occurs hyperplasia of the lymph tissue of the posterior pharyngeal region, which is often associated with nasal or pharyngeal catarrh, with frequent "colds," and with mouth-breathing. The redundant tissue forms a lobular mass which often blocks the nasopharyngeal passage. These adenoids may contain tuberculous lesions.

The Pharynx.

The lesions of the pharynx similar to those just described as involving the nasal cavities are reviewed on page 746.

The Larynx and Trachea.

Malformations.

The larynx and trachea may be absent. The larynx may be abnormally large or small; the epiglottis also may be too large or too small, or may be cleft. Small larynges are observed in castrates or persons with genital hypoplasia. There may be communications between the trachea and the esophagus, and then the pharynx generally ends in a cul-de-sac, and the esophagus opens into the trachea. A diaphragm may be formed across the anterior or posterior portion of the larynx.[2] There may be imperfect closure of the original branchial arches, so that there are fissures in the skin leading into fistulæ which open into the pharynx or trachea. The fissure in the skin is small and is situated about an inch above the sternoclavicular articulation, usually on one or both sides, more rarely in the middle line. Individual cartilages, as the epiglottis, or one or more rings of the trachea, may be absent, or there may be supernumerary rings. The trachea may divide into three main bronchi instead of two, and in that case two bronchi are given off to the right lung and one to the left. The trachea may be on the left side of the esophagus or behind it.

HEMORRHAGE.

In trauma and acute inflammatory processes, in syphilis and tuberculosis, and when tumors are present, especially carcinoma and some forms of vascular papilloma, there may be hemorrhage from the larynx. It may occur also under the general favoring conditions, such as hemophilia, scurvy, and various abnormal conditions of the circulation leading to local or general hyperemia.[3]

EDEMA OF THE GLOTTIS.

This is a condition in which there is an accumulation of serous fluid in the submucosa of the upper part of the larynx. This may be due to simple circulatory disturbances, local or general, or it may be inflammatory in character. The greatest accumulation of fluid is in places in which the submucous tissue is abundant and loose in texture, as in the posterior wall of the epiglottis, in the arytenoepiglottidean folds, and in

[1] *Hasslauer*, Arch. f. Laryngol. u. Rhinol., 1900, x, 60 (bibl.). For a discussion of polypoid tumors of the nasal septum, see *Onodi*, ibid., 1914–15, xxix, 30.

[2] *Glas*, Wien. klin. Wchnschr., 1908, xxi. 603.

[3] For a study of hemorrhage of the larynx, see *Rhodes*, Jour. Am. Med. Assn., 1904, xliii, 1284.

the false vocal cords. The swelling of these parts may be so great as to occlude the air passage. After death the edematous swelling may largely disappear, owing to the evaporation of the exudate; but the mucous membrane may be left unusually wrinkled and flabby.

Edema of the glottis is comparatively infrequent in association with such heart, kidney, and lung lesions as lead to general edema. It is, on the contrary, frequent in connection with various forms of laryngeal inflammation, either following extensions of local infection or in the infectious diseases, such as diphtheria, scarlet fever, smallpox, and typhoid fever. An acute edema may follow the administration of the iodides in susceptible persons. It may occur in drunkards or others who are poisoned and fall asleep in a sitting posture so that the head drops sharply forward with constriction of the neck. Under these conditions the individual may die from asphyxia with no obvious lesion accounting for it other than the edema of the glottis.

INFLAMMATION. (Laryngitis.)

Acute Catarrhal Laryngitis.—This occurs as an independent process in common "colds." It may be a complication of the infectious dis-

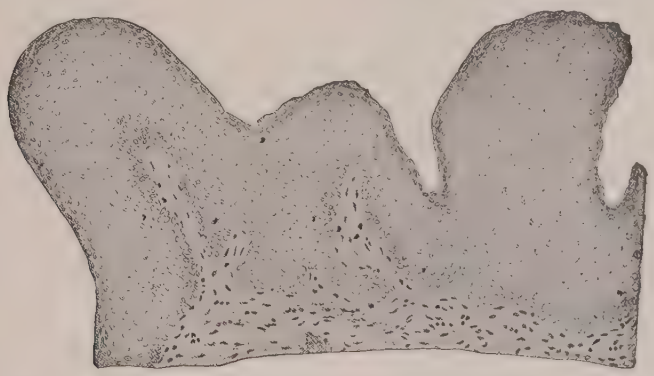


FIG. 399.—LOCALIZED HYPERPLASIA OF THE EPITHELIUM AND SUBMUCOUS CONNECTIVE TISSUE OF THE FALSE VOCAL CORDS.

The section shows a portion of a small rough wart-like or papillary growth.

eases, especially whooping-cough and measles, or may be induced by the inhalation of irritating vapors and of hot steam and smoke. The inflammation varies in its intensity in different cases. The mucous membrane is at first congested, swollen, and dry; then the mucous glands become more active and an increased quantity of mucus is formed. There is desquamation of the superficial epithelial cells, while through emigration leucocytes may infiltrate the submucosa, and together with mucus and desquamated epithelium form the exudate. There may be edema of the glottis. All of these lesions may disappear with complete restoration of the mucous membrane.

After death the congestion of the mucous membrane marking an acute form of the disease frequently disappears altogether.

Chronic Catarrhal Laryngitis.—This may follow repeated attacks of acute inflammation or be the result of the persistent inhalation of harmful substances. It may accompany chronic hyperemia from cardiac or vascular lesions. It may be associated with syphilis and tuberculosis.

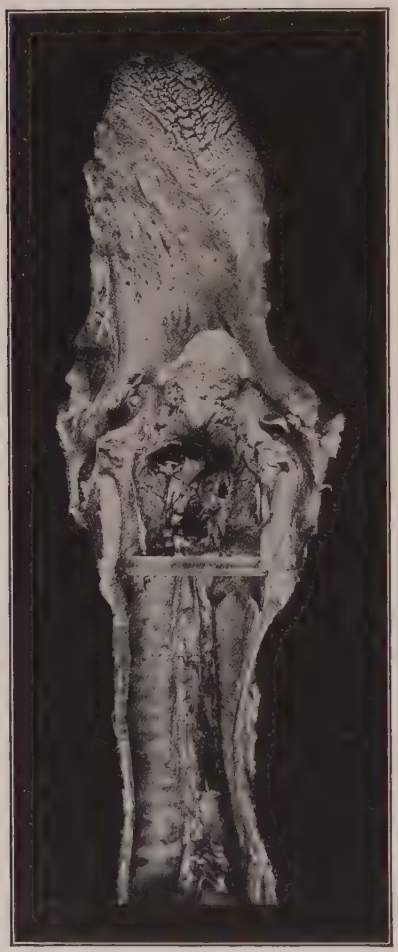


Fig. 400.—Diphtheria of the Larynx and Trachea.

The membrane extends from the epiglottis down to the bifurcation of the trachea.

The surface of the mucous membrane is dry or coated with mucopus. The epithelium is thickened in some places, thinned in others, or in places entirely destroyed. The submucosa may be infiltrated with cells, diffusely thickened, or form little papillary outgrowths; it may be thinned, or necrotic and ulcerated.

The mucous glands may be swollen and prominent. The inflammation may extend to the perichondrium of the cartilages, which may become necrotic. In chronic laryngitis there may be a more or less diffuse thickening of the epithelium often associated with a hyperplasia of the submucous tissue. This is called *pachydermia diffusa.* A similar process, if localized, may lead to larger and smaller wart-like excrescences—*pachydermia verrucosa* (Fig. 399). Carcinoma has been observed to develop on such a lesion.[1]

Pseudomembranous Laryngitis (Croupous Laryngitis).—This occurs most frequently as the characteristic local lesion in diphtheria, of which the Bacillus diphtheriæ is the excitant (see page 319). It may, however, be incited by the Streptococcus pyogenes and other bacteria, and not infrequently accompanies other infectious diseases, scarlatina, typhoid fever, and the exanthemata (see page 345). The false membrane may be continuous with a similar structure in the pharynx, and it may extend down into the bronchi (Fig. 400).

Phlegmonous Laryngitis.—Suppurative inflammation involving the mucosa and submucosa is usually secondary to catarrhal, croupous, tuberculous, or syphilitic laryngitis; or it may be associated with pyemia, erysipelas, smallpox, or typhoid fever. It may follow mechanical

[1] *Fränkel, B.*, Arch. f. Laryngol. u. Rhinol., 1903, xiii, 1.

injury from a foreign body. It is not uncommon on the posterior surface of the epiglottis or in the arytenoepiglottidean folds, and may be associated with edema of the glottis. Abscesses may form which rupture into the larynx, or extend into the neck, the pharynx, or the esophagus.

Tuberculous Laryngitis.—This lesion is most frequently associated with pulmonary tuberculosis. Early in the process there is a formation in the submucosa of miliary tubercles together with more or less new connective tissue and lymphocytes; with this is a catarrhal inflammation with an exudate of mucus, pus cells, and desquamated epithelium (Fig. 401).

As coagulation necrosis of the subepithelial tubercles occurs, ulcers are formed, often with an increase of the catarrhal exudate. These

FIG. 401.—TUBERCULOUS LARYNGITIS.
The epithelium on the surface has ulcerated over a small area. The tubercle is situated in the subepithelial layer.

lenticular ulcers are shallow, oval areas, and are especially abundant on the epiglottis. The process may extend so as to involve the walls of the larynx, and necrosis of the cartilages may follow. Adjacent ulcers may become confluent so that considerable areas of the mucous membrane may be destroyed (Fig. 402). Lupus, also, may occur in the larynx.

Syphilitic Laryngitis.—This form of inflammation may have the ordinary characters of an acute or chronic catarrhal inflammation, or may be productive in character with the formation of new tissue in the stroma of the mucous membrane. The new tissue is principally composed of small cells which often degenerate and become necrotic. In this way the mucous membrane of the larynx and the tissues beneath are thickened in some places and destroyed in others, giving rise to erosions and ulcers. At one stage, the lesion may be papillary. These changes are especially marked in the upper portion of the larynx. If the perichondrium be involved there may be necrosis of the laryngeal cartilages. Gummata

are infrequent. Owing to the cicatricial contractions of healed syphilitic ulcers there may be great deformity of the larynx.

Lesions of the **trachea** are often associated with those of the larynx and are in general similar in character.

TUMORS OF THE LARYNX AND TRACHEA.

LARYNX.—**Retention cysts** of the mucous glands of the larynx may form sacs projecting into its cavity.

Papilloma, single or multiple, is the most common form of benign tumor of the larynx (Fig. 403); it is most frequent upon the vocal cords (*singers' nodes*) and is usually associated with chronic inflammation.

Adenoma, fibroma, lipoma, myxoma, and **angioma** occasionally occur. An extremely rare lesion is the **amyloid tumor** which is found most fre-

FIG. 402.—TUBERCULOUS LARYNGITIS.
The posterior surface of the epiglottis and the adjacent tissue are involved in tuberculous ulcers.

quently in the larynx and next most commonly in the tongue.[1] Remains of thyroid tissue have been found in the larynx.

Enchondromata grow from the normal cartilages and are usually multiple and sessile; they may project into the cavity of the larynx.[2]

Fusiform or spheroidal-cell **sarcomata** of the larynx have been seen in a considerable number of cases, both in children and in adults.

Carcinoma, which is usually of the epitheliomatous type, may originate in the larynx, most commonly upon the false vocal cords. Its

[1] *Seckel,* Arch. f. Laryngol. u. Rhinol., 1912, xxvi, 1 (bibl. covering amyloid tumors in general); *Mannasse,* Virchows Arch., 1900, clix, 117; *Pollak,* Ztschr. f. Laryngol., Rhinol., etc., 1914–15, vii, 24 (bibl.); *Willimann,* Arch. f. Laryngol. u. Rhinol., 1912, xxvi, 395.

[2] *Salomonsen,* Arch. f. Laryngol. u. Rhinol., 1913–14, xxviii, 454 (bibl.).

spread is very slow, and it usually involves only the lymph-nodes in its immediate neighborhood.

Primary **carcinoma** of the epiglottis is extremely rare, but has been described.[1]

A unique case of **metastatic hypernephroma** in the larynx has been reported.[2]

Cysts of the larynx have been described.[3]

TRACHEA.—Tuberculous or otherwise altered bronchial lymph-nodes may enter the trachea by ulceration and obstruct the passage.

Tumors of the trachea are of rare occurrence, but growths similar to those in the larynx have been occasionally found.[4]

FIG. 403.—PAPILLOMA OF THE LARYNX.
The left vocal cord is involved in the lobulated growth. A tracheotomy opening is seen below the tumor.

The Bronchi and Lungs.

The Bronchi.

HEMORRHAGE.

In hemorrhage from the bronchi the source of the blood is often to be sought in the parenchyma of the lung (see page 687) or in a ruptured aneurysm. But hemorrhage from the bronchial walls may occur in tuberculous or other forms of ulceration, chronic bronchitis, malignant tumors, etc.

INFLAMMATION. (Bronchitis.)

Acute Catarrhal Bronchitis.—This is frequently associated with a similar process in the trachea. It is characterized by hyperemia and swelling of the mucous membrane, with the formation of exudate, which usually consists largely of mucus formed by the hypersecretion of the mucous glands or degeneration of the epithelial cells. Mingled with this are exfoliated and more or less degenerated epithelium from the mucous membrane, leucocytes from the dilated vessels of the submucosa, varying numbers of red blood-cells, and bacteria.

The microscopic appearances differ in different parts of the bronchial tubes in accordance with the differences in structure. Mucous glands,

[1] *Mayer*, Arch. f. Laryngol. u. Rhinol., 1913, xxvii, 588 (bibl.).
[2] *Menzell*, Arch. f. Laryngol. u. Rhinol., 1912, xxvi, 264.
[3] *Glas*, Arch. f. Laryngol. u. Rhinol., 1906–07, xix, 285 (bibl.).
[4] *Broman, J. R.*, Jour. Cancer Res., 1924, viii, 394.

when these are present, may reveal great functional activity, and their ducts may be distended with mucus which, often mingled with exfoliated and degenerated cells, streams out upon the surface. Swelling and proliferation of the connective-tissue cells and endothelium of the vessels of the submucosa, edema, and emigration from the dilated vessels are often marked. The leucocytes may be seen making their way through the epithelium into the other exudates upon the surface. The epithelium may be loosened, single or clustered cells falling off here and there, or shreds of cells may exfoliate together (see Fig. 404).[1] The deeper spheroidal epithelia, the so-called mother cells from which the new ciliated cells on the surface are formed in both physiological and pathological regeneration, usually remain in place upon the basal membrane. In the small bronchi whose walls are thin, little else may be seen than an irregular exfoliation of the epithelium. On the other hand, the smaller

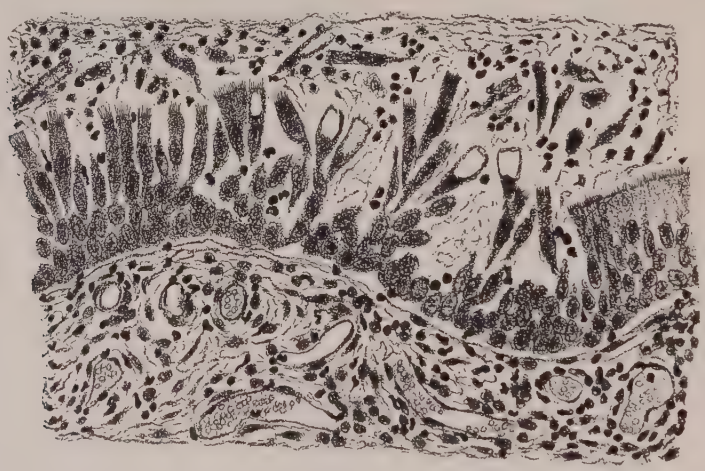


FIG. 404.—ACUTE CATARRHAL BRONCHITIS.

This section of a small portion of the bronchial wall shows considerable exfoliation of the epithelium, but many of the deeper so-called "mother cells" remain in place. There are swelling of the connective-tissue cells and congestion of blood-vessels in the submucosa, with edema and emigration of leucocytes. Some of the leucocytes are passing through the epithelium to mingle with the mucous exudate and exfoliated cells in the lumen of the bronchus. Some of the ciliated cells show the "beaker" shape with a homogeneous interior indicating the production of mucus within them.

bronchi may be much involved and their lumina filled with exudate; when this, which has been called "*capillary bronchitis*," occurs, the inflammatory process usually involves the adjacent and associated territories of lung tissue, constituting one of the important forms of bronchopneumonia. In some forms of bronchitis the exudate may consist largely of pus—"*purulent bronchitis*."

Atelectasis of corresponding tracts of the lung may follow the occlusion of the bronchi with exudate. As recovery advances, the submucosa assumes its normal thickness and character and the epithelium is regenerated from the cells of the deeper layers.

[1] For a study of physiology and pathology of ciliated epithelium of the respiratory organs, see *Lommel*, Deutsch. Arch. f. klin. Med., 1908, xciv, 365.

Various forms of *bacteria* may be associated with acute bronchitis, and under favorable conditions are presumably the excitants of the lesions; the etiological relationship has, however, not yet been experimentally established. The most common forms of bacteria are Streptococcus pyogenes, the pneumococcus, Staphylococcus aureus, and the influenza bacillus.[1]

Chronic Catarrhal Bronchitis.—This form of bronchitis may be the sequel of one or more attacks of acute bronchitis. More frequently it is associated with emphysema, heart disease, interstitial pneumonia, phthisis, pleuritic adhesions, or the inhalation of irritating substances. There is in most cases a constant production of mucus, pus, and serum in considerable quantities, and these inflammatory products may have a very foul odor. Less frequently these products are very scanty—*dry catarrh*. The epithelium is deformed and desquamating, with a production of new cells in the deeper layers. There may be epithelial

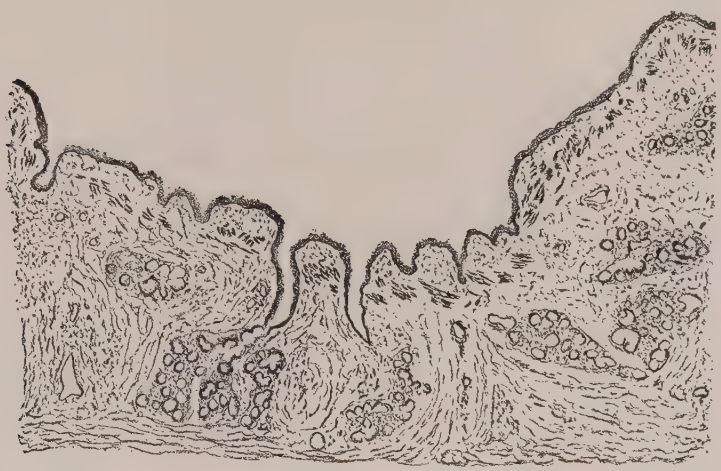


FIG. 405.—CHRONIC BRONCHITIS WITH MODERATE BRONCHIECTASIA.

This transverse section of a portion of the wall of a dilated bronchus shows atrophy of the epithelium; fibrous hyperplasia of the submucosa with the formation of longitudinal ridges on the interior of the tube (cut across in this section); thickening of the wall of the bronchus and atrophy of the mucous glands.

hyperplasia or atrophy; the mucous glands are large or atrophied; there may be hyperplasia or atrophy of the submucosa; the muscularis may show hypertrophy or atrophy. These changes in the fibrous and muscular elements of the walls lead to the so-called "trabeculation" of their inner surfaces (Fig. 405). Obliterating arteritis of the associated vessels may occur. These changes in the walls of the bronchi may lead to bronchiectasia.

Acute Pseudomembranous Bronchitis—Croupous Bronchitis—may occur with croupous laryngitis, as a lesion of diphtheria, with lobular pneumonia, and sometimes without these associations. The bronchi

[1] For a study of the bacteria found in bronchitis, see *Ritchie, W. T.*, Jour. Path. and Bacteriol., 1901, vii, 1; also *Karcher*, Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 244.

are lined or filled with a mass of fibrin, pus, and desquamated epithelium. Fibrin and pus may also be found beneath the epithelium and infiltrated in the stroma.

Chronic Fibrinous Bronchitis is attended with the formation in one or more bronchi of masses of fibrin which are expectorated by the patient in the form of branching casts of the bronchi (Fig. 406). After death the bronchi are said to be but little altered from the normal.[1]

Curschmann has described under the name *"bronchiolitis exudativa"* a form of bronchitis in which small threads and bands of gray or yellow, partly transparent, coagulated material are formed in the small bronchi —"Curschmann's spirals." These sometimes occur in pneumonia. In different forms of bronchitis, especially in those associated with asthma,

FIG. 406.—CHRONIC FIBRINOUS BRONCHITIS.
Fibrinous casts of the bronchi, similar to those shown in the photograph, were coughed up at irregular intervals for several years.

the exudation may contain numerous octahedral bodies—Charcot-Leyden crystals—and also a very large number of eosinophile cells.

Tuberculous Inflammation of the bronchi frequently occurs in connection with pulmonary tuberculosis. The lesion may be miliary or larger involvement of the walls may lead to ulceration.

Syphilitic Inflammation may lead to ulcers and to distortions and stenosis through cicatrization.

BRONCHIECTASIA.

Dilatations of the bronchi may be cylindrical, fusiform, or sacculated. The sacculated dilatations are usually the largest, and communicate with one side of the bronchus. The peripheral portion of the bronchus may be obliterated; the bronchus leading to the cavity may be of normal size, or dilated, or stenosed, or even completely obliterated. Such sacculated dilatations may reach a very large size and may communicate with each other. Dilatations are apt to occur under conditions which

[1] For a résumé and bibliography, see *Bettmann, M.*, Am. Jour. Med. Sc., 1902, cxxiii, 304.

interfere with the integrity of the bronchial wall and also those which partially close a bronchus, such as thoracic aneurysm.

In acute general bronchitis and bronchopneumonia in children, cylindrical dilatation of a number of the medium-size bronchi often occurs.

In the persistent bronchopneumonia of children such dilatations may reach a still greater development.[1] Chronic bronchitis may lead to cylindrical or sacculated dilatations, sometimes of great size.

Occlusion of some of the bronchi, consolidation of portions of the lung, and extensive pleuritic adhesions may also lead to bronchiectasia (Fig. 407).

FIG. 407.—MULTIPLE BRONCHIECTASIÆ WITH INTERSTITIAL PNEUMONIA.
Portion of anterior free border of lungs. From an adult after unresolved lobar pneumonia.

The walls of bronchiectatic cavities may be lined with mucous membrane, which, however, is apt to undergo various changes as the process advances. Thus the subepithelial layer may be vascular and cellular and thrown into folds, or it may be thin and dense. The epithelium is often irregular, sometimes irregularly thickened, sometimes thin, or it may be largely absent. The glands, muscle, and cartilages of the walls of the bronchi may disappear through atrophy. The presence of certain forms of bacteria in the exudate in bronchiectasia may lead to an offensive putrefactive process and even to gangrene, especially if the drainage

[1] For a study of bronchiectasia in children, see *Lapin*, Arch. f. Kinderh, 1903, xxxvii., 406.

is not good. Moulds may be present, and acid-fast bacilli of the smegma group are often found in the sputum.

In acute and chronic phthisis the tuberculous inflammation of the walls of the bronchi often gives rise to sacculated dilatations, which expand with time and become still larger by the destruction of the adja-

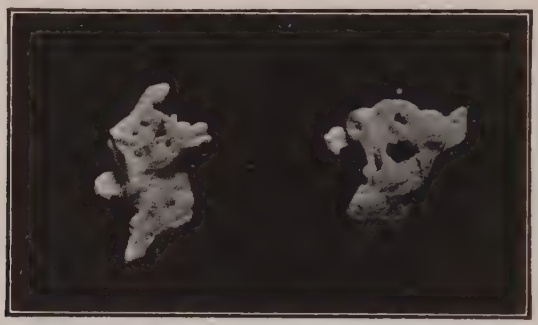


Fig. 408.—Lung Stones. (*From a case of Tuberculous Bronchitis.*) These calcified masses were found in the dilated bronchi.

cent lung tissue—tuberculous bronchiectasiæ. These are most frequent in the upper lobes, while the non-tuberculous form is most often seen in the lower portion of the lung. Enlargement of the tips of the fingers and toes is not infrequent in chronic bronchiectasiæ either simple or of tuberculous origin. (See p. 1066 under pulmonary dystrophy.)

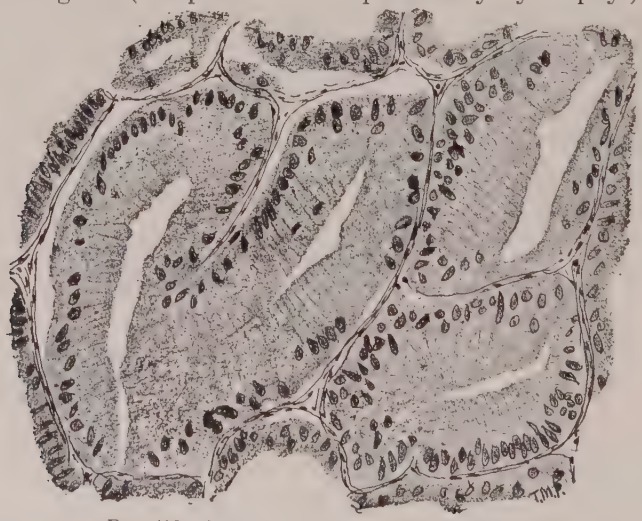


Fig. 409.—Primary Adenoma of the Bronchi.

Occlusion of the bronchi, either partial or complete, may be caused by tumors, parasites, especially ascaris, foreign bodies, exudates, etc., or by destructive lesions in the walls. Calcified masses called "*lung stones*" (Fig. 408) may be found. (See also p. 736 ref.)

TUMORS.

Primary tumors of the bronchi are rare. **Lipoma, chondroma,** and **fibroma** have been observed. **Sarcoma** is rare, but may occur, especially in its spheroidal-cell form or as an extension of sarcomata from the mediastinum. **Adenoma** (Fig. 409) and **primary carcinoma**[1] are also uncommon. **Epithelioma** occurs, and is assumed to be derived from bronchial epithelium which has undergone a metaplasia into the squamous type. Such tumors may remain small and be noticeable clinically only from the metastases which they produce. When the bronchus is obstructed by the tumor, secondary dilatation below the point of closure occurs, with the production of large bronchiectatic cavities.[2] **Secondary carcinoma** is not unusual and may involve also the trachea or the lungs.

Plasmocytoma of the upper air passages has been described.[3]

Fig. 410.—Tuberculous and Caseous Bronchial Lymph-nodes.

The nodes are much enlarged and press upon the larger bronchi.

LESIONS OF THE TRACHEAL AND BRONCHIAL LYMPH-NODES.

The tracheal and bronchial lymph-nodes may be the seat of a variety of lesions which, owing to their situation, as well as for other reasons, are of considerable practical importance. They may be enlarged from hyperplasia in acute infectious diseases; by the development in them of tumors; in leukemia, in Hodgkin's disease, and with especial frequency in tuberculosis (Plate V). They may become pigmented from inhaled coal or other dust and may atrophy or become fibrous or calcified.[4] In cheesy degeneration following tuberculosis (Fig. 410), or in suppurative inflammation, perforation may take place into the air passages, the esophagus, the pulmonary blood-vessels, or aorta, or into the pericardial or pleural cavities;[5] in this way hemorrhage or secondary inflammatory processes or gangrene may occur. Death may occur from pressure upon the trachea by tumors of the adjacent

[1] *Weller*, Arch. Int. Med., 1913, xi, 314 (bibl.); *Kreglinger*, Frankfurt. Ztschr. f. Path., 1913, xii, 135; *Davis*, Tr. Chicago Path. Soc., 1913–15, ix, 156.

[2] *Ernst, P.*, Zieglers Beitr., 1896, xx, 155.

[3] *Wachter*, Arch. f. Laryngol. u. Rhinol., 1913–14, xxviii, 69 (bibl.).

[4] For the association of pigmentation and tuberculosis of the bronchial lymph-nodes and the pleura, see p. 728. For a study of alleged intestinal origin of lung pigment, see *Montgomery, E. M.*, Jour. Med. Research, 1910, N. S. xviii, 111.

[5] See *Sternberg, C.*, Wien. klin. Wchnschr., 1905, xviii, 1214.

lymph-nodes. Sudden death may occur from perforation into the trachea. Pressure upon the pulmonary veins may lead to pulmonary edema. The bronchial lymph-nodes are very important as distributing centers of infectious microorganisms, and particularly as points of lodgment of tubercle bacilli, which have been gathered from the pulmonary air spaces, from the pharynx, or elsewhere.[1]

The Lungs.

Malformations.

One or both lungs may be wanting or only partially developed. One lung is sometimes converted into a number of sacs formed of dilated bronchi, while the lung parenchyma is undeveloped. Supernumerary bronchi are recorded.

The lobes may be subdivided by deep fissures, accessory lobes may be present, or an accessory lung may be present. An accessory lung in the abdominal cavity has been described.[2] There may be, with absence of part of the wall of the thorax, hernia of the lung. There may be transposition of the lungs, with similar changes in the position of the heart and the abdominal viscera.

INJURIES—PERFORATIONS.

Severe contusions of the thorax may produce rupture of the lungs, with extravasations of blood into the pleural cavities.

The lungs may be wounded by puncture from a fractured rib and by penetrating weapons and projectiles. Such injuries often lead to bleeding into the lung tissue, followed by inflammatory changes. The lungs, however, exhibit a considerable degree of tolerance for such injuries, many perforating bullet wounds healing in a few days unless a large vessel has been severed.

Collections of pus in the pleural cavities, the mediastinum, the liver, the spleen, the kidneys, and the peritoneal cavity may perforate the lungs. See also Hydropneumothorax.

DISTURBANCES OF CIRCULATION.

It is very useful to anticipate a study of the diseases of the lungs by an examination of the circulation in the lung of a curarized frog on the Thoma frog-plate (see page 129). In no other way can one gain so vivid a conception of the complexity and abundance of the circulatory mechanism.

Anemia.—The lungs may be anemic in connection with a general anemia of the body; or from compression of a part or a whole organ, as by pleural exudates, tumors, or new-formed fibrous tissue; from occlusions of blood-vessels or in atrophy of these in emphysema.

[1] Consult for summary of lesions of bronchial lymph-nodes, *Hall, J. N.*, Philadelphia Med. Jour., 1900, vi, 1059 (bibl.). See also *Northrup, W. P.*, New York Med. Jour., 1891, liii, 203; *Bovaird, D.*, ibid., 1899, lxx, 1; and *Harbitz*, Jour. Infect. Dis., 1905, ii, 143. See also statistics of *Hand*, Proc. Philadelphia Path. Soc., 1903, vi, 132. For an excellent résumé concerning normal and pathological tracheal and bronchial lymph-nodes, see *Marfan, A. B.*, Bouchard and Brissaud, Traité de Médicine, Paris, 1901, vii, 525; also *Zuber*, Grancher, Comby, and Marfan, Traité des maladies de l'enfance, Paris, 1904, iii, 578. For a study of the relation of the bronchial lymph-nodes to the lymph-vessels of the thorax see *Weleminsky, F.*, Berl. klin. Wchnschr., 1905, xlii, 743. For a study of the relationship of the cervical and bronchial lymph-nodes, see *Beitzke, H.*, Virchows Arch., 1906, clxxxiv, 1.

[2] Consult *Vogel, R.*, Virchows Arch., 1899, clv, 235; and *Hammar, J.*, Zieglers Beitr., 1904, xxxvi, 518.

Tuberculous Bronchial Lymph-Nodes.

The nodes are enlarged and caseous, with areas of commencing softening. An isolated tubercle in the lung tissue above the enlarged nodes indicates a local dispersion of the tubercle bacilli. The lung was hardened in alcohol.

Hyperemia and Edema.

Hyperemia may occur as the result of the inspiration of irritating gases; from the presence of toxic substances in the blood; in early phases of inflammation, or as the result of such an occlusion of vessels in one part as causes the accumulation of blood in another.

On the other hand, hyperemia of the lung is often due either to some hindrance to the exit of blood through the pulmonary vein, such as mitral stenosis or insufficiency, or to enfeeblement of the ventricular contractions, as in fatty degeneration of the heart muscle or interstitial myocarditis. In the last hours of life the feeble action of the heart disposes to pulmonary congestion. The position of the body upon the back in bed favors an accumulation of blood in the posterior portions of the lungs—*hypostatic congestion*. Hyperemic lungs are in varying degrees

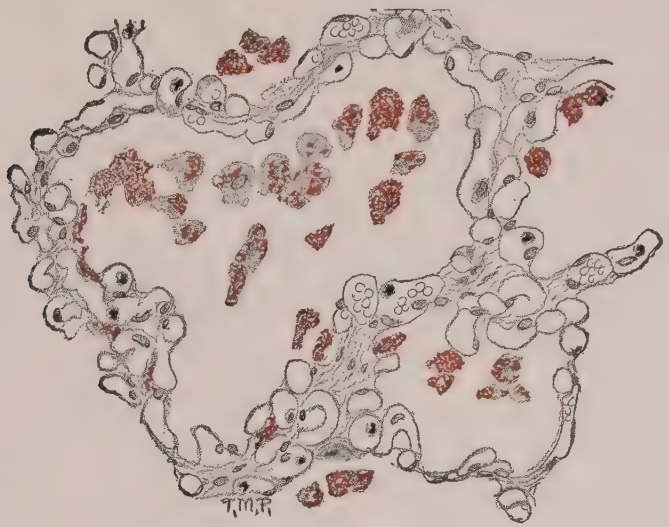


Fig. 411.—Chronic Congestion of the Lung. (Brown Induration.)
Showing dilated capillaries of the walls of the air vesicles and hematogenous pigment in the exfoliated epithelial cells of the air vesicles.

darker and heavier than normal; an unusual amount of blood flows from the cut surface. Edema fluid also is often present. Red blood-cells often pass through the capillary walls in hyperemia, and these with more or less exfoliated epithelium may be found in the air vesicles.

Chronic Congestion.—In prolonged hyperemia of the lungs, notably in connection with lesions of the mitral and aortic valve, or degeneration or dilatation of the left ventricle, the veins and capillaries, especially the capillaries, become permanently distended, pouched, and elongated, so that they often stretch in loops into the air spaces (Fig. 411). Red blood-cells find their way from the contorted vessels by diapedesis or small hemorrhages into the air vesicles or interstitial tissue of the lung. Here decomposition of the hemoglobin leaves brownish pigment particles

which may remain free or be taken into cells. In the air vesicles the epithelial cells usually desquamate in considerable numbers, and take up the pigment in varying amount. This pigment gives to the lungs a peculiar brownish pink or salmon color. The appearance of these lungs may be modified by hemorrhagic infarctions, by preexisting emphysema or edema, or by exudative inflammation. Associated with these changes there is usually a new formation of fibrous tissue, so that the lung becomes indurated, leathery, and dry, and collapses less readily than normal. This condition is often called *brown induration* of the lung. This formation of fibrous tissue is analogous with that which occurs in other organs, such as the kidney and liver in chronic congestion. Emigration of leucocytes is not infrequently associated with diapedesis from the dilated capillaries, and these, with the desquamated epithelium, may accumulate in the air vesicles.

EDEMA OF THE LUNGS.

This condition is rarely independent, but is usually associated with other lesions of the circulatory or respiratory systems. It may be circumscribed or involve one or both lungs. The lungs in pronounced edema do not collapse, as is usual on opening the thorax. They may appear translucent. Fluid runs or is readily squeezed from the cut surfaces.

In edema of the lungs the vesicles contain a clear, sometimes foamy albuminous fluid, occasionally tinged with blood, usually mixed with exfoliated vesicle epithelium. Leucocytes and red blood-cells may also be present. The edematous fluid may be present in the bronchi and in the interstitial tissue of the lungs. Edema is often associated with hyperemia, and like this may vary in different parts of the lung. On the other hand, there may be extensive edema without overfilled blood-vessels; these in excessive edema may indeed be nearly empty and compressed. Edema of the lungs may occur in general infections and intoxications, or in association with local inflammatory processes.

It may be associated with cardiac and renal lesions. It may be a part of general dropsy or exist independently of this. It frequently occurs in the last hours of life—agonal edema. Edema of the lung may occur suddenly without the obvious inciting accompaniments above noted and may be fatal. In such instances the edema is due to an increased permeability for fluid of the pulmonary capillaries.[1] Fatal edema of the lungs may be associated with fat embolism.[2]

The studies of Welch[3] show that with diminished force exerted by the left side of the heart, the vigor of the right remaining unimpaired, edema of the lungs may follow.[4]

[1] See *Krehl*, Clinical Pathology, Eng. trans. Philadelphia, 1905, p. 122.
[2] *Connell*, Jour. Am. Med. Assn., 1905, xliv, 612.
[3] *Welch, W. H.*, Virchows Arch., 1878, lxxii, 375; résumé by *Meltzer*, Am. Med., 1904, viii, 391.
[4] For a study of edema of the lungs based on numerous cases, see *Coplin*, Proc. Path. Soc., Philadelphia, 1906, ix , 77; also *Riesman*, Am. Jour. Med. Sc., 1906, cxxxiii, 88. For a study of the disturbances of circulation in the lungs under various abnormal conditions see *Esser, J.*, Centralbl. f. inn. Med., 1901, xxii, 97 (bibl.).

HEMORRHAGE AND INFARCTIONS.

Hemorrhage.

Hemorrhage into the lung tissue and air spaces of the lungs may occur from trauma, from pulmonary infarction, from rupture of aneurysm, in acute infectious diseases and intoxications, in scurvy and hemophilia, in asphyxia from brain lesions or other conditions, or from tuberculous ulcerations involving the blood-vessels. Multiple ecchymoses may occur in fat embolism.

Hemorrhage is of frequent occurrence in excessive hyperemia of the lungs, notably in connection with mitral stenosis and insufficiency. Under these conditions the extravasation of blood may take place by diapedesis or by rhexis. The accumulations of blood may be single or multiple, localized or diffuse, dense and firm, or, when edema is present, soft and fluid in character. During the last hours of life, owing to enfeeblement of the heart, extravasation of blood may occur which sinks to the posterior dependent portions of the lungs.

Thrombosis, Embolism, Infarcts.

As a result of thrombosis or embolism of the pulmonary artery, *hemorrhagic infarcts* may be formed. They are not very common in the lungs because the supply of blood is through both the pulmonary and bronchial arteries, so that even with stoppage of the pulmonary artery by a thrombus or embolus, hemorrhagic infarcts are not necessarily formed. When, however, the pulmonary circulation is faulty as in various cardiac lesions, hemorrhagic infarcts are more apt to form as the result of embolism or thrombosis of the pulmonary artery.

These infarcts are often multiple, usually circumscribed, and rounded or wedge-shaped, from the size of a walnut to that of an orange. They are of dark red color, hard and unaerated, with the air spaces distended with blood, and are often surrounded by a zone of inflammatory exudate. They may be situated in any part of the lungs, but are most common in the lower lobes. At the apices of the infarcts, the occluding thrombus or embolus may be discovered. When, as is usually the case, they are near the surface of the lungs, a circumscribed inflammation of the pleura often occurs. The air spaces within the infarcts are filled with blood and the capillaries distended.

Such infarcts may be followed by death; they may become gangrenous, or if the emboli or thrombi be not infectious, the blood may become absorbed, and, especially in the smaller forms which are more often due to embolism, they may be gradually changed into a smaller mass of pigmented fibrous tissue.[1]

A large part of the lungs may be involved in hemorrhage due to thrombosis of large trunks of the pulmonary artery. Hemorrhagic

[1] For a study of experimental infarction of lung, see *Karsner* and *Ash*, Jour. Med. Research, 1912 N. S. xxii, 205. Also *Mann, F. C.*, Jour. Exper. Med., 1917, xxvi, 387.

infarctions from thrombosis or embolism are most frequent in lungs which are the seat of chronic congestion. The most common source of the emboli of the pulmonary artery is the right heart or peripheral thrombi.[1] After surgical operations especially in the pelvic region, and also after injury, thrombi may form in the veins with subsequent embolism of the pulmonary artery. Such embolism is a frequent cause of sudden death (see page 42).

ATELECTASIS.

In atelectasis the walls of the air spaces lie together, either because they are collapsed or compressed, or because, as in congenital atelectasis, the lungs, or portions of them, have not been expanded in respiration.

FIG. 412.—VESICULAR EMPHYSEMA.
Showing enlargement of the air spaces and thinning of their walls.

In fetal or *congenital* atelectasis, defects in the respiratory mechanism or blocking of the air passages may be responsible for the unaerated condition which may affect only parts of a lung or a whole organ. The atelectatic portions of the lungs are dark red in color and of fleshy consistence.[2]

Atelectasis may, on the other hand, be *acquired*, either in childhood or in adult life. In young children collapse of portions of the lung is of frequent occurrence, through occlusion of bronchi by inflammatory exudate. The region thus cut off is gradually deprived of air, and as the blood continues to circulate, becomes dark red and firm in texture. *Compression atelectasis* may be due to exudates, tumors, etc., in the pleural cavities. Under these conditions the portion of lung involved may

[1] For a fuller consideration of embolism and thrombosis of the pulmonary artery consult *Welch*, Albutt, System of Medicine, 1909, vi, 691. See also *Keen*, System of Surgery, 1906, i, 444; also *Aschoff*, *de la Camp*, *von Beek*, and *Krönig*, Beitrage zur Thrombosefrage, Leipzig, 1912.

[2] Collapsed lungs, from their red color and fleshy consistence, are often spoken of as "carnified."

be paler than normal from the pressing out of the blood. In adults, large or small portions of lung tissue may collapse from occlusion of a bronchus by exudate or stenosis, by paralysis of the vagus, or in long-continued feebleness of respiration. Edema may be associated with collapse.

Atelectasis may resolve by an early admission of air to the collapsed region. On the other hand, if prolonged, fibrous tissue may form and the involved portion may be finally converted into a cicatricial mass, sometimes containing bronchiectatic cavities.

FIG. 413.—INTERLOBULAR EMPHYSEMA OF LUNG. Child two months old. After whooping-cough.[1]

EMPHYSEMA.

Vesicular Emphysema.—In forcible inspiration or expiration through obstruction of the air passages, in coughing, in the use of wind instruments or in glass-blowing, or with consolidation or compression of portions of the lungs, the walls of the air spaces of the lungs may be more or less distended, either in circumscribed regions or over large areas of the lungs. Inasmuch, however, as every performer on wind instruments or every glass blower does not develop emphysema[2] the assumption has to be made that other factors than mere increased intrapulmonary pressure play a part, even though subordinate. The occurrence of emphysema in families points in the same direction; hence, a defective lung structure is often assumed as a precursor to the final change. Whether such defects in the elastic or connective tissue of the lung parenchyma exist has not yet been proved. The distention of the lung tissue may develop rapidly producing an acute emphysema.

If the conditions which induce emphysema are persistent, as in chronic bronchitis with difficult respiration and coughing, atrophy of the walls

[1] For a fuller description of this case, see *Northrup, W. P.*, Am. Jour. Med. Sc., 1883, lxxxvi, 147.
[2] *Hoffman, F. L.*, Jour. Industrial Hygiene, 1920, ii, 1.

of the air vesicles and alveolar passages may take place—chronic emphysema. The walls become thinner and are often perforated; adjacent air spaces coalesce, so that larger and smaller irregular, thin walled cavities are formed (Fig. 412). Destruction of the capillary network of the atrophied walls occurs, and the lung may thus become pale and anemic. As a rule, the distention of the air spaces is most marked along the anterior margins of the lungs, but it may be more general. Through the atrophy of the elastic tissue of the lungs, when the lesion is general and advanced, these organs do not collapse when the chest is opened. They appear pale, are dry and soft, and pit on pressure by the finger.

FIG. 414.—INTERSTITIAL EMPHYSEMA OF THE LUNG OF A CHILD.
The irregular darker areas in the lower lobe indicate the air largely in the interlobular septa.

In addition to the changes in the lung, deformation of the thorax is evident if the emphysema is of long standing. The sternum arches forward, the ribs are held in a position of full inspiration, and there is often a kyphosis. Premature ossification of the costal cartilages occurs.[1] Hypertrophy of the accessory muscles of respiration is not infrequent. The heart may be pushed upward. Some pathologists consider that the emphysema is secondary to the thoracic changes and possibly consequent alteration in the pulmonary circulation.[2]

[1] *Löschcke*, Deutsch. med. Wchnschr., 1911, xxxvii, 916; Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 435; and *Salis, H. V.*, Frankfurt. Ztschr. f. Path., 1910, iv, 399.

[2] For bibl. of the newer views on emphysema, see *Pässler, H.*, Über Lungen Emphysem, Deutsch. Klin., 1909, xii, 409.

The microscopic picture is that of varying degrees of atrophy; desquamation and fatty degeneration of the vesicle epithelium are common.

As already indicated, emphysema of the lungs is often associated with chronic bronchitis and with chronic asthma. With this may be more or less hyperplasia of the interstitial tissue. Dilatation or hypertrophy of the wall of the right ventricle is common. Chronic endarteritis of the pulmonary vessels may be associated with emphysema. There may be chronic venous congestion of the abdominal viscera and dropsy. Delafield held that the more esssential lesion in some forms of emphysema is the development of new connective and elastic tissue with which dilatation of the air vesicles and atrophy of their walls are in varying degrees associated.[1]

In old age, atrophic processes in the lungs may be associated with dilatation and mergence of the air spaces. This is called senile emphysema. The lungs contract when the thorax is opened, the tissue is friable, and the elastic and connective tissues are diminished. Excessive emphysema, however, may be present in young children following whooping-cough (Fig. 413), or in some instances may be congenital in origin.

Interstitial Emphysema.—Rupture of the walls of the air spaces may permit the escape of air into the interstitial tissue of the lungs (Fig. 414). It is seen after whooping-cough and laryngeal diphtheria, or when artificial respiration has been violently applied in conditions where the bronchi are contracted, such as anaphylaxis consequent upon injection of antitoxic sera. Rupture of the pulmonary pleura may admit air into the mediastinum and thence into the tissues of the neck. Gas may form after death in the interstitial tissue of the lungs, from the presence of the Bacillus aërogenes capsulatus or other putrefactive bacteria.

GANGRENE.

Circumscribed gangrene occurs in the form of one or more rounded or irregular masses of variable size. The gangrenous portion of lung is at first brown and dry. The surrounding lung tissue is congested or edematous, or infiltrated with blood, or inflamed. If the gangrenous focus is near the pleura, the latter will be coated with fibrin. Gradually the gangrenous portion of lung assumes a dirty green color and a putrid odor. It becomes soft, disintegrated, and separated from the surrounding lung. The blood-vessels may be obliterated by thrombi, or eroded so that there are profuse hemorrhages.

Such a gangrenous process may extend to the adjacent lung tissue, or a zone of gray or red hepatization or of connective tissue may be formed. The fluid from the gangrenous lung may pass into the bronchi and be expectorated; or it may run from one bronchus into another and incite new gangrenous foci or diffuse gangrene. The pulmonary pleura may be perforated and a gangrenous pleurisy produced. Gangrene may follow lobar or bronchopneumonia, especially such phases of the latter as result from the inspiration of foreign material containing microorganisms from

[1] See also *Orsós*, Zieglers Beitr., 1907, xli, 95.

the mouth; it may arise from infectious emboli in the lungs, or by an extension of a gangrenous process from an adjacent part. It may be associated with esophageal diverticula.[1]

Diffuse gangrene may follow the circumscribed form; it may complicate lobar pneumonia or occur as an independent condition. A large part of a lobe or of an entire lung becomes greenish, putrid, and soft, and the pulmonary pleura is inflamed. There may be hemorrhages from eroded vessels. There may be general septicemia.

Various forms of bacteria may be present in gangrenous areas of the lungs. Among the more common are Streptococcus pyogenes, Staphylococcus pyogenes, pneumococcus, and various saprophytic microorganisms,[2] among them the fusiform bacilli and the spirochete of Vincent.[3]

INFLAMMATION. (Pneumonia, Pneumonitis.)

General Considerations.

The lungs, like the gastrointestinal canal, while in a topographic sense within the body, are still in communication with the exterior, and are thus more directly exposed to various deleterious changes than those structures and organs wholly enclosed by living tissues. The situation has necessitated the development of protective mechanisms of great efficiency which dispose of much of the material entering the respiratory tract.

The air impinging upon the moist surface of the tortuous passages of the nose loses a very considerable part of its dust and bacteria. Similar cleansing takes place in the throat, larynx, and trachea, so that at the end of inspiration the air has been so freed from its floating particles that it emerges in the expired breath practically free from dust and germs.

Much particulate matter is swept away from the lungs by the cilia of the cells of the air passages. Some of it is carried off through the lymphatics. Living bacteria may reach the lungs and remain there for a short time but are rapidly removed by the phagocytes or destroyed by lytic agents. Soot, when it reaches the lungs either directly or through the gastrointestinal tract by the intermedium of the lymphatics, collects in the interlobular lymphatics which are closely connected with the branches of the pleural plexus[4] (Fig. 416). Along the subpleural lymph-vessels are numerous islets of lymphoid tissue and often a few small lymph-nodes.[5]

LUNG ABSCESS.

Lung abscess is closely related to gangrene of the lung causally, and in some instances inseparable from it except by minor differential points. These differences are probably due in part to the method of production of the two conditions and in part to secondary infective organisms. Gangrene is apt to occupy a much more extensive portion of the lung, to lack a sharply circumscribed wall, and to be dependent upon thrombosis of the vessels with or without pulmonary pneumonic processes. Abscess of the lung which has in the last few years become a very important pulmonary

[1] See *Stark*, Arch. f. Verdauungskr., 1901, vii, 1.

[2] See for "acid-proof" bacilli in gangrene, *Ophüls, W.*, Jour. Med. Research, 1902, N. S. iii, 242.

[3] *Buday*, Zieglers Beitr., 1910, xlviii, 70 (bibl.).

[4] *Councilman, W. T.*, The Lobule of the Lung and Its Relation to the Lymphatics, Boston Jour. Med. Sc., 1900, iv, 165. For a study of the comparative histology of the lungs of domestic animals, see *Müller*, Arch. f. mikros. Anat., 1906, lxix, 1.

[5] See for a study of pleural lymph-nodes and lymphoid tissue *Heller*, Deutsch. Arch. f. klin. Med., 1895, lv, 141. For a comprehensive résumé of the normal and pathological physiology of the lungs, see *Heinz, R.*, Handbuch der exper. Path. u. Pharmakol., Jena, 1906, ii.

lesion in connection with the great development of surgery of the oral cavity, is a rather local lesion, generally sharply circumscribed and occupying less of the lung than the gangrenous process. It is now perfectly evident that the causation of such abscesses is in a large percentage of examples the aspiration of septic material into the bronchus. Certainly half of the cases belong in this group.

Tonsillectomy is responsible for a greater proportion of these examples; the extraction of teeth a smaller proportion. After these come various operations on the naso-pharynx and mouth; more rarely abscesses are secondary to septic foci elsewhere in the body and in infrequent instances they may be secondary to carcinoma, tuberculous and syphilitic processes not necessarily primarily affecting the lungs.

Abscesses of the type under consideration occur most frequently in the right lung, in the lower lobes and in the peripheral portion of the viscus. About one-fourth are multiple. They are considerably more frequent in males than in females. The lesion may involve chiefly one or more bronchi which dilate and form bronchiectatic cavities, or the lesion may involve a considerable portion of the lung as a suppurative process or the abscess may exist as a small strictly localized suppurative process not closely related to the bronchi. The latter types are usually secondary to pneumonia. When infected material is inhaled there is set up a local inflammatory process in the wall of the bronchus in which the material is deposited The process may and frequently does remain limited to this situation and it is even possible that the foreign material is ultimately coughed up and no further change occurs. Usually, however, the wall of the bronchus which is infiltrated with exudate softens and under the irritative coughing which follows the presence of such a substance in the lumen of the respiratory passages, the wall is expanded and a bronchiectatic cavity partially lined with mucous membrane forms. Usually there is a certain amount of pneumonia in the neighboring pulmonary alveoli. If the infecting organisms are sufficiently destructive to the surrounding tissues, the abscess may spread away from the bronchus into the lung.

Fig. 415.—Abscess of Lung.

The necrotic types of broncho-pneumonia which have become more frequent in recent years are responsible for an increase in the occurrence of abscess. In this type and more rarely in the lobar variety it is noticed that the pneumonia does not resolve and the tissues when examined show a sharply defined cavity of softened lung surrounded by a wall made up of necrotic material with more or less fibrous tissue resulting from a reaction of the organ to the destructive processes and usually outside of this irregular patches of more or less chronic pneumonia with the desquamation of the alveolar epithelium. Such epithelial cells may be filled with hematoidin granules. The cavity is usually filled with thick pus mixed with mucus from the bronchial secretion. When the lung is opened the cavity usually collapses owing to the lack of a rigid demarcation zone.

The characteristic features of the sputum in abscess of the lung are the odor and the presence of occasional shreds of pulmonary tissue. The sputum differs greatly in consistency. It may be thin and purulent, or thick and tenacious, and varies also in color with the stage of the disease and the amount of altered blood pigment which it contains. When the hemoglobin of the blood has been thoroughly decomposed by the action of the putrefactive bacteria which chronic abscesses often contain, it may be a dark brown or even a black color. When the sputum is allowed to stand it separates into three layers, a frothy upper, a cloudy middle, and a heavy lower of sedimented pus. The bacterial flora is very varied. In the early stages pure cultures of streptococci, staphylococci, or pneumococci may be obtained and

FIG. 416.—LUNG SHOWING TUBERCLES WITH PIGMENTATION IN THE PLEURA
At the lower left-hand portion the lobules of the lung are outlined by the thickening of the walls of the lymph-channels and of the interlobular septa.

in the rarer types aspergillus, streptothrix, actinomyces, or even blastomyces, may be found.

The characteristic symptoms are cough with free expectoration of large quantities of pus. This pus may or may not be offensive in odor. Clubbed fingers are frequent in the chronic cases. Skiagraphs may show a cavity with changing fluid level.

The course of the disease is extremely chronic and death results in about 75 per cent. of the untreated cases. Others go on with recurring febrile attacks due to the extension of the inflammatory processes and may die from a fresh pneumonia, empyema, or cerebral abscess.

Acute Lobar Pneumonia. (*Fibrinous Pneumonia—Croupous Pneumonia.*)

This is an infectious disease incited most frequently by the Diplococcus pneumoniæ[1]. It is especially characterized by an exudative inflammation in which red and white blood-cells, serum, and fibrin accumulate in the air spaces of the lungs, usually involving, especially in adults, the whole of one lobe or lung or portions of both lungs.[2] Toxemia from the absorption of poisons formed locally in the lungs is an important and often most significant factor in the disease. The pneumococcus is usually widely disseminated in the blood.

During the first hours of the inflammation the capillaries of the air spaces are congested, the lung is edematous, firmer than normal, but not markedly consolidated. The air spaces contain varying numbers of leucocytes, red blood-cells, serum, and fibrin (Fig. 417). The epithelial cells lining the air vesicles may be swollen, they sometimes proliferate, and are usually detached in considerable numbers. Catarrhal bronchitis and pleuritis may at this time develop. This is called the stage of "congestion" or "engorgement" and may last for a few hours or for several days.

As the process continues, red blood-cells, but especially polymorphonuclear leucocytes, and fibrin accumulate in the air spaces and smaller bronchi, so that the portion of lung involved becomes solid and friable, somewhat resembling the liver in color and consistence; hence the term "*red hepatization*" which has been used to indicate this condition. The cut surface of the consolidated portion is dry and coarsely granular, the granules being plugs or casts of exudate in the air spaces. A light scraping of the cut surface of the lung with the knife readily removes these granules or plugs of exudate, which consist largely of fibrin and leucocytes with red blood-cells and exfoliated epithelium (Fig. 418). The relative amount of leucocytes, red blood-cells, and fibrin in the air spaces

[1] We shall use here as synonymous the names Diplococcus pneumoniæ and pneumococcus; when pneumococcus is used the pneumococcus of Fraenkel is referred to. For a description of this organism and methods of grouping for therapeutic purposes, see *Avery*, *Chickering*, *Cole*, and *Dochez*, Acute Lobar Pneumonia: Prevention and Serum Treatment, Monograph No. 7, Rockefeller Inst., New York, 1917; and p. 248.

[2] The clinical course and the morphological characters of the inflammation of the lungs associated with the Diplococcus pneumoniæ are so typical that we seem justified in limiting the term lobar or fibrinous pneumonia to this condition, even though inflammations of the lungs due to other excitants are occasionally lobar in extent and may have a fibrinous exudate, and though exceptionally the pneumococcus inflammation itself fails to reach lobar proportions.

varies greatly, sometimes one, sometimes the other, preponderating (Fig. 419). The fibrin fibrils often coalesce or swell, forming homogene-

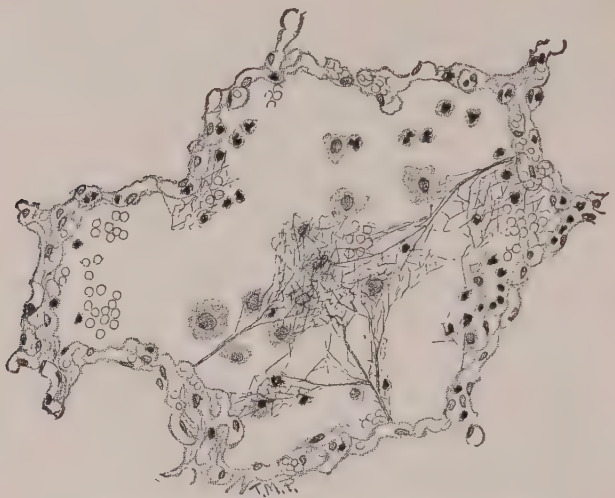


FIG. 417.—ACUTE LOBAR PNEUMONIA—EARLY STAGE.
This single air vesicle shows congestion of the capillaries in the walls, and a small amount of exudate, fibrin, leucocytes, red blood-cells, and exfoliated epithelium.

ous, irregular masses. On staining, large numbers of pneumococci may be found mingled with the other elements or within the cells of the exudate. While the general appearance of the lung in this stage is red,

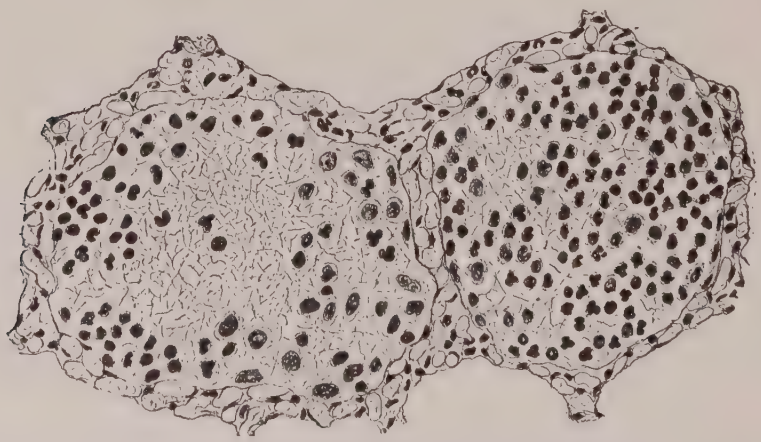


FIG. 418.—ACUTE LOBAR PNEUMONIA—STAGE OF "RED AND GRAY HEPATIZATION."
The air vesicles are filled with exudate consisting largely of leucocytes, fibrin, and serum with a few epithelial cells.

it is often mottled with gray and frequently is not uniformly solid. Although the capillary blood-vessels are compressed, they for the most part remain pervious; but thrombosis is not infrequent. Fibrinous

pleuritis is commonly present, and the interstitial tissue of the lung, while usually free from exudate, may be edematous and contain a few leucocytes and some fibrin.

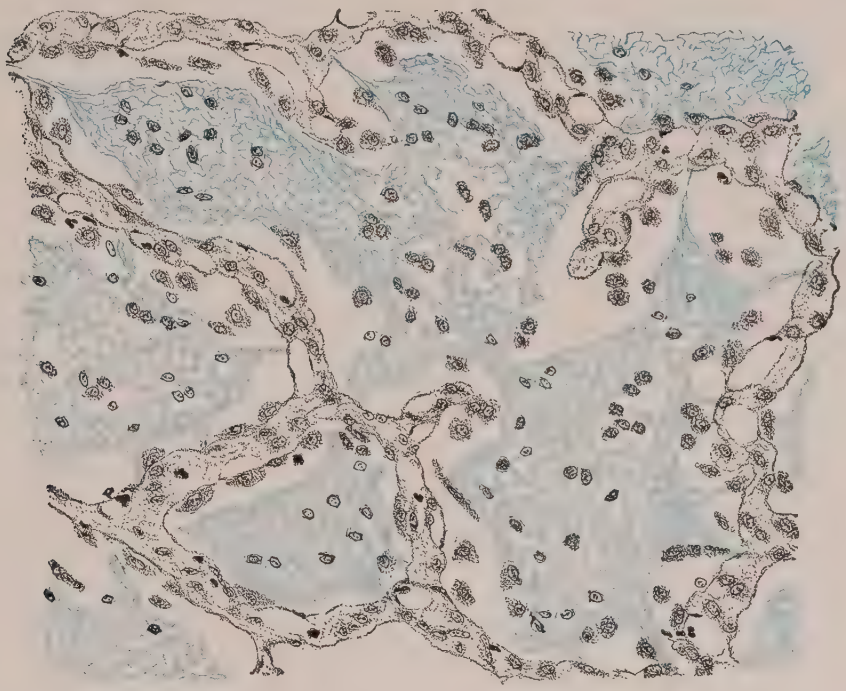


FIG. 419.—ACUTE LOBAR PNEUMONIA.
Showing fibrinous exudate stained by Weigert's method.

The quantity of exudate in the lung is often very large, sometimes three to four or even six pounds in weight.

In the usual course of events the red blood-cells now lose their hemoglobin, the exudate begins to soften, and the lung assumes a grayish color —*gray hepatization* or *commencing resolution*. The leucocytes and exfoliated epithelium undergo granular and fatty degeneration[1] or necrosis, and these with the fibrin soften and disintegrate (Fig. 420). The cut surface of the lung is now moister and less granular, and is often covered with a grumous fluid.

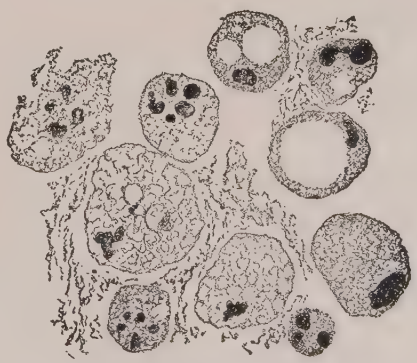


FIG. 420.—EXUDATE FROM THE LUNG IN RESOLVING LOBAR PNEUMONIA.
The cells show various phases of granular and fatty degeneration with fragmentation of the nuclei and disintegration of the cell bodies.

[1] See, on fatty degeneration of pneumonic exudates, *Christian, H. A.*, Jour. Med. Research, 1903, N. S. v, 109 (bibl.).

The plug-like quality of the exudate is lost and the lung tissues appear gray and translucent and the whole inflammatory mass is removed in a few days by autolytic softening of the exudate,[1] part of which is now expectorated, the rest absorbed. As this progresses the involved portion of the lung becomes aerated and the epithelium lining the air spaces is regenerated. The walls of the alveoli, the bronchi and the perivascular tissues in lobar pneumonia are not involved in the infection, hence repair is rapid. Often the whole process requires only a day or two.

While it is customary and convenient to describe definite stages of lobar inflammation of the lung—red and gray hepatization and resolution—these in fact not only merge gradually into each other, but often co-exist in different parts of the lung. The process of reparation also usually occurs irregularly, so that a lung in resolution may show side by side in neighboring air spaces well-formed cellular and fibrinous exudate, degenerated exudate, and various phases of epithelial cell repair.[2]

The nature of the characteristic crisis[3] in pneumonia, is not clear. It is not accompanied by obvious changes in the pulmonary exudate.

For the evidence of communicability of pneumonia see page 255.[4]

Associated Lesions in Other Organs.[5]—Fibrinous or serofibrinous pleuritis, usually with slight but often with voluminous exudate, commonly accompanies lobar pneumonia. Catarrhal and fibrinous bronchitis is also usually associated with the pneumonic process. Pericarditis and endocarditis are not infrequent complications; meningitis occasionally occurs. The excitant of these complications is usually the pneumococcus.[6]

Chromatolysis of the ganglion cells, albuminous degeneration in the kidney, liver, and heart, hyperplasia of the bronchial lymph-nodes, together with leucocytosis, fever, and frequent serious enfeeblement of the heart action, are marks of toxemia. The bronchial lymph-nodes may contain, especially in the perifollicular sinuses, and often within phagocytes, red blood-cells, cell detritus, and pneumococci brought from the lungs; fibrin is frequently also present.

In lobar pneumonia in young children, in those enfeebled by acute and chronic disease, and in the aged, the lungs are often less uniformly consolidated and less dense and hard than in vigorous adults. When lobar pneumonia occurs in lungs already the seat of chronic lesions, such as chronic congestion, emphysema, interstitial pneumonia, or tuberculo-

[1] For a study of the chemistry of resolution of the exudate, see *Simon*, Deutsch. Arch. f. klin. Med. 1901, xx, 604. See also *Levene*, Jour. Am. Med. Assn., 1906, xlvi, 774, 866.

[2] For a study of the histology of acute lobar pneumonia with bibl., see *Pratt, J. H.*, Johns Hopkins, Hosp. Rep., 1900, ix, 265.

[3] See for a study of the crisis, *Tchistovitch*, Ann. Inst. Pasteur, 1904, xviii, 304 (bibl.); also, for discussion of opinion, p. 249.

[4] See, for a general study of communicability, *Edsall* and *Ghriskey*, Tr. Col. of Phys., Philadelphia, 1904, xxvi, 6; and *Dochez* and *Avery*, Jour. Exper. Med., 1915, xxii, 105.

[5] See for résumé of statistics of complications *Kerr*, Tr. Chicago Path. Soc., 1903, v, 274. Also, for an analysis of four hundred and eighty-six cases, *McCrae*, *Fyshe*, and *Ainley*, Am. Med., 1904, vii, 135.

[6] For a study of pneumococci in the blood in pneumonia see *Rosenow*, Jour. Infect. Dis., 1904, i, 280 (bibl.); also *Dochez, A. R.*, Jour. Exper. Med., 1912, xvi, 680.

sis, the gross appearances of the organs may differ in various ways from those of uncomplicated pneumonia.

While Diplococcus pneumoniæ is the regular excitant of lobar pneumonia, other bacteria—see below—are not infrequently associated with it, sometimes, though by no means always, leading to clinical complications and to modifications of the appearance of the lesion. Predisposition of the individual is an uncommonly conspicuous and important factor in the etiology of this as other forms of pneumonia, so that, as is well known, exposure, fatigue, etc., may induce the favoring bodily conditions under which the pneumococcus becomes harmful. The experiments upon animals are most conclusive in demonstrating that intrapulmonary injections of pneumococcus cultures, which may be entirely without obvious effects in a healthy animal, may induce exudative inflammation or become quickly fatal after such exposure to cold or fatigue or injury, or to the action of drugs, as interferes with the integrity of the blood or locally damages the pulmonary tissues.[1]

Delayed Resolution after Lobar Pneumonia ("Organizing Pneumonia").—Instead of undergoing resolution, the fibrinous and cellular exudate in the air spaces in lobar pneumonia may persist, and by a process similar to that which is called organization of a thrombus (page 38) may be gradually replaced by new vascular fibrous tissue. New connective-tissue cells grow out from the walls of the air spaces into the exudate; these cells become elongated. Intercellular fibrils develop, and long masses or bands of this new tissue, often containing blood-vessels, may extend for considerable distances through the air channels of the lung (Fig. 421). These may gradually coalesce with the walls, and together with an interstitial connective-tissue growth may lead to a fibrous consolidation of the lung.

Delafield described such an intra-alveolar formation of connective tissue leading to fibrous induration of lobes of the lung and occurring as an independent lesion apart from the exudative form of lobar pneumonia.

Concurrent Infection and Suppurative Inflammation of the Lung Following Lobar Pneumonia.

Although, as stated above, Diplococcus pneumoniæ usually occurs alone in typical lobar pneumonia, it may be accompanied by the Streptococcus pyogenes or hemolyticus, by the Staphylococcus pyogenes, and occasionally by other microorganisms. The exact significance of these mixed or concurrent infections in lobar pneumonia is not always clear. But instead of the usual resolution there may be gangrene; or suppuration of the interstitial lung tissue with the formation of abscess may occur. In such cases Streptococcus pyogenes and Staphylococcus pyogenes aureus or putrefactive bacteria may be present with the pneumococcus in the exudate.

[1] For a comprehensive résumé of studies on experimental pneumonia, see *Wadsworth, A. B.*, Jour Exper. Med., 1912, xvi, 54, 78 (bibl.). For experimental pneumonia in dogs by bronchial insufflation, see *Lamar* and *Meltzer*, ibid., 1912, xv, 133. For study of lesions produced by bronchial insufflation of streptococci, see *Wollstein* and *Meltzer*, ibid., 1913, xviii, 548.

The clinical type of pneumonia caused by the Friedländer bacillus does not differ greatly from that due to the pneumococcus, except in its almost regularly fatal course, the mortality being about 85 per cent. The organism can be found in the sputum and in the blood.

The lung, when incised, is not granular, as in pneumococcus pneumonia, but is slimy, and a stringy, clear or bloody mucus can be scraped from the cut section This consists chiefly of the bacteria with their mucoid capsules. There is less fibrinous exudate and fewer leucocytes and red blood-cells in the alveolar exudate, than in pneumococcus pneumonia. The center of the consolidated area frequently undergoes softening, but, as a rule, does not break into the large bronchi and give rise to bronchiectases.[1]

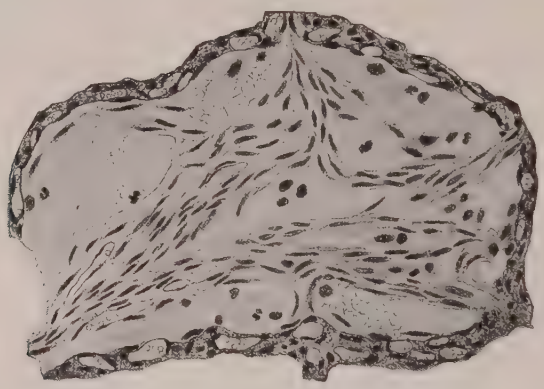


FIG. 421.—"ORGANIZING" PNEUMONIA—DELAYED RESOLUTION AFTER LOBAR PNEUMONIA. Anastomosing fascicles of fusiform connective-tissue cells lie within the air vesicle and are continuous with similar new formations in adjacent air spaces.

Suppurative inflammation of the interstitial tissue of the lungs may involve not only the larger fibrous-tissue bands, but the walls of the air vesicles and other air spaces. It is often called "purulent infiltration." From the cut surface of the lungs in resolving lobar pneumonia a grumous fluid resembling pus often exudes, and this is sometimes mistaken for a mark of interstitial suppuration of the lung.

Suppurative inflammation of the interstitial tissue of the lung may occur without association with lobar pneumonia.

LOBULAR PNEUMONIA AND BRONCHOPNEUMONIA.

In distinction from that common form of pulmonary inflammation induced by the Diplococcus pneumoniæ, which as we have seen is usually lobar in character, there are exudative inflammations of the lungs, due to many different excitants, which are "patchy" or "lobular" in extent, the consolidated areas varying in size from such as are scarcely visible to those several centimeters in diameter.[2] These patches of lobu-

[1] *Toenniessen*, München. med. Wchnschr., 1911, lviii, 2608.

[2] The term lobular does not refer exclusively to the anatomical "lobule" of the lung, since the masses or patches of consolidation often embrace several lobules or parts of these.

lar consolidation often join and merge, so that solidification of whole lobes or lungs is not uncommon. But the mottled, uneven surface and color of the lungs on section, and the usual absence of the peculiar granulation ordinarily suffice for the distinction, even to the naked eye, of the lobar from the coalescent lobular forms of exudative pneumonia.

It is convenient to recognize several types of lobular exudative pneumonia, although the character of the exudate is not distinctive.

Bronchopneumonia.—Lobular Pneumonia with Inflammation of the Smaller Bronchi.

This most important type of lobular pneumonia frequently develops in connection with, and as an extension of that form of inflammation of the smaller bronchi commonly called "capillary bronchitis." At first dark red in color, the lobular areas of consolidation in bronchopneumonia become more gray at the center through degeneration of the exudate, while the advance of the process in the periphery is marked by a less solid, redder zone. On section of the fresh lung these areas (Fig. 422)

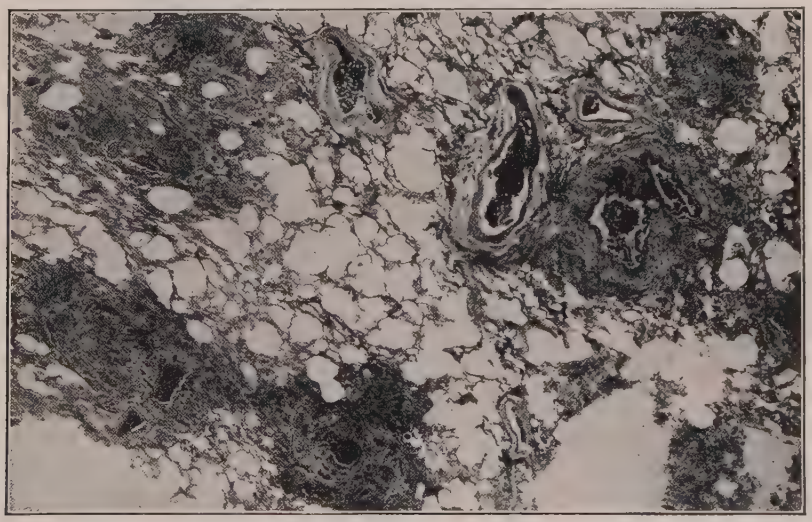


FIG. 422.—BRONCHOPNEUMONIA IN AN ADULT.
Showing several areas of consolidation with the central bronchus filled with exudate—stained dark in the section from which the photograph was made.

usually project somewhat above the general surface, and at their centers the involved bronchi may appear as lighter spots, from which pus may exude or be easily pressed out. Such areas may coalesce, forming larger consolidations. The exudate, which more or less completely fills the air spaces (Fig. 423), consists of serum, old and new-formed epithelial cells from the walls of the air spaces, red blood-cells, and often fibrin and polymorphonuclear leucocytes (Fig. 424) with various forms of microorganisms. As a rule, however, fibrin and leucocytes are not so abundant as in the exudate of lobar pneumonia. Giant cells are frequently found in the alveoli in the bronchopneumonia of children.[1]

[1] *Hecht*, Zieglers Beitr., 1910, xlviii, 263 (bibl.).

Mucus and bronchial epithelium may be aspirated into the air spaces and mingled with the exudates.

Bronchopneumonia involves a direct extension of the inflammatory process from the bronchi to the contiguous lung tissue, so that there is both an interstitial and an exudative pneumonia about the bronchial tubes, the whole forming the lobular areas of consolidation (Fig. 425). This

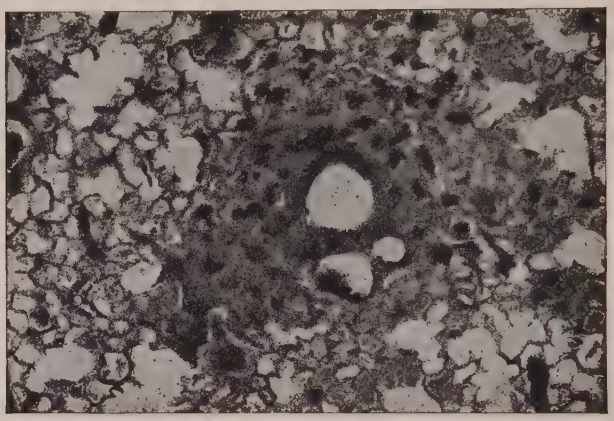


FIG. 423.—BRONCHOPNEUMONIA IN A CHILD.
The section shows a single lobular area of consolidation with its bronchus whose thickened wall merges with the surrounding zone of exudative pneumonia.

involvement of the bronchial wall in inflammation with a direct extension of the process to the surrounding lung tissue has been urged especially by Delafield as the process to which the term *bronchopneumonia* should be *par excellence* applied.

Between the consolidated areas there may be atelectasis of lung tissue from the occlusion of the smaller bronchi with exudate. When the consolidated areas are situated at the surface of the lungs, fibrinous pleuritis may be present over the affected regions.

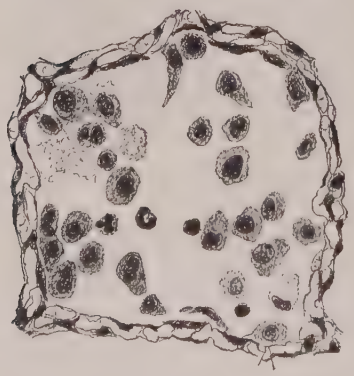


FIG. 424.—BRONCHOPNEUMONIA—EXUDATE IN A SINGLE AIR VESICLE.

This form of bronchopneumonia is frequent in children, sometimes as an independent process, but often associated with or following diphtheria, scarlatina, measles, etc.[1] It occurs also in adults, either as a complication of infectious diseases such as typhoid fever, smallpox, influenza, measles, etc., or as a primary process. It may occur in the aged or in those enfeebled by wasting diseases.

Resolution may take place in the areas of bronchopneumonia by proc-

[1] MacCallum has recently called attention to the frequent occurrence of this type of pneumonia among soldiers. See *Cole* and *MacCallum*, Jour. Am. Med. Assn., 1918, lxx, 1146 and *MacCallum*, Rockefeller Institute Monographs No. 10, New York, 1919.

esses of cell degeneration and absorption identical with those through which restoration is secured in lobar pneumonia. If, however, resolution in bronchopneumonia does not presently take place, and the lesion persists, dense connective tissue is apt to form about the bronchi and in the interstitial tissue of the lungs, which may lead to induration and distortion of the organs, atelectasis, chronic bronchitis with dilatation of the bronchi, etc. A photograph of a section of such a chronic or "persistent" bronchopneumonia is reproduced in Fig. 426. Empyema due to the Streptococcus hemolyticus is a frequent complication.

Other Forms of Lobular and Bronchopneumonia.—There are forms or types of lobular pneumonia in which serum and epithelial cells with more or less fibrin and leucocytes collect in the air spaces of a limited

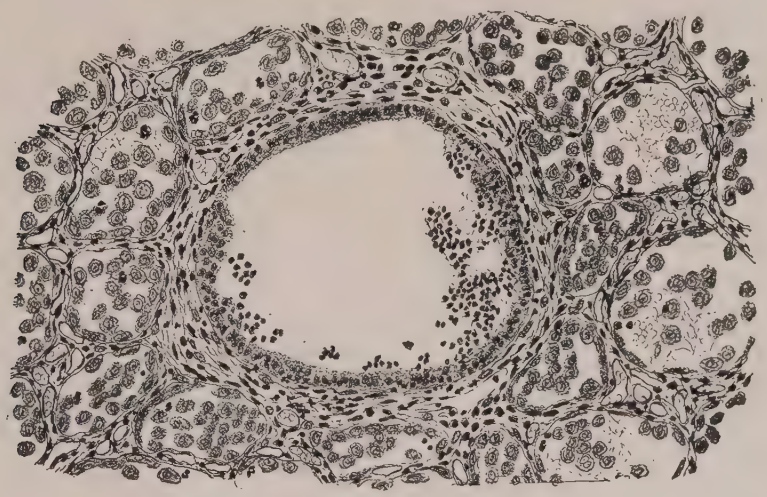


FIG. 425.—BRONCHOPNEUMONIA—CHILD.

Showing slight change in the epithelium of the bronchus; a purulent exudate in the lumen; thickening of the wall of the small bronchus, and exudate in the adjacent air vesicles.

region without primary bronchitis and without involvement of the walls of the bronchi and air spaces.

In one type of lobular pneumonia and bronchopneumonia the exudate may consist largely of pus cells which infiltrate the walls of the air spaces and bronchi as well as fill the air spaces themselves. This type of inflammation may be induced by the aspiration in feeble persons of irritating substances or bacteria-containing material of various kinds, particles of food, saliva, etc. This is called *aspiration pneumonia* and may result in necrotic or gangrenous processes in the involved regions of the bronchi and lungs. Again there may be circumscribed areas of exudative pneumonia, often suppurative in type and involving the walls of the air spaces, called lobular pneumonia of *hematogenous origin*, or *pyemic* or *septic pneumonia*. Thus, *abscesses* of the lungs may be formed. Such abscesses are of occasional occurrence after tonsilectomy.[1]

[1] *Clendening, L.*, Jour. Am. Med. Assn., 1920, lxxiv, 941; and *Fisher, L.*, and *Cohen, A. J.*, ibid, 1921, lxxvii, 1313.

In the lobular pneumonia of bubonic plague the exudate consists largely of blood and plague bacilli.[1]

In the aged or those long in bed in an enfeebled condition, hyperemia and edema with more or less exudate, usually epithelial in character, may develop in the dependent posterior portions of the lungs—*hypostatic congestion* and *hypostatic pneumonia.*

There is a peculiar and rare form of bronchopneumonia associated with necrosis in which forms of streptothrix have been isolated which

Fig. 426.—Persistent—Chronic—Bronchopneumonia.

are undoubtedly the excitants of the disease.[2] Actinomyces is also an occasional excitant of bronchopneumonia.

In all these forms of lobular pneumonia edema and atelectasis of uninvolved portions of the lung may occur.[3]

It is evident that in lobular pneumonia the infectious agent may reach the lungs either through the air passages or through the blood- or lymph-vessels, and that differences in the portals of entry as well as in the nature and virulence of the excitant and the susceptibility of the indi-

[1] Consult *Flexner, S.*, Tr. Assn. Am. Phys., 1901, xvi, 481.

[2] Consult *Norris* and *Larkin*, Jour. Exper. Med., 1900, v, 155; see also discussion on page 262.

[3] For a type of lobular pneumonia in which the alveolar contents simulate giant cells, see *Karsner* and *Meyers*, Arch. Int. Med., 1913, xi, 534.

vidual have an important bearing upon both the course of the disease and the morphology of the lesion.

The Excitants of Lobular and Bronchopneumonia.—The excitants of bronchopneumonia and other types of lobular pneumonia are most frequently Streptococcus pyogenes (Fig. 427), the pneumococcus, Staphylococcus pyogenes, the typhoid, diphtheria, influenza, and plague bacilli, and the pneumobacillus of Friedländer; the streptothrix, above mentioned, and other bacteria have been occasionally found.[1] Pathogenic moulds may be excitants of acute forms of lobular pulmonary inflammation.

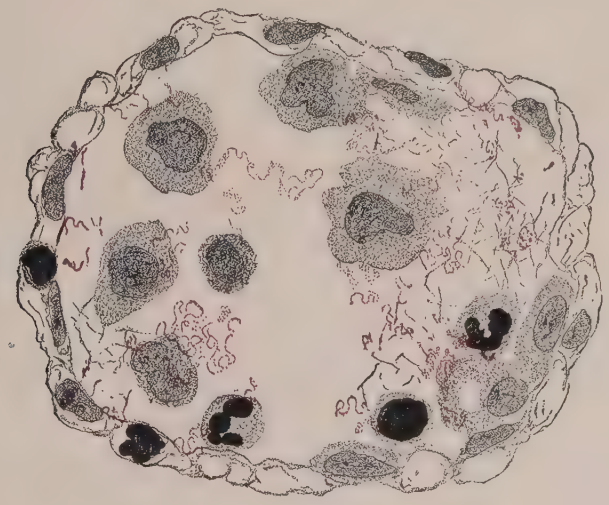


Fig. 427.—Air Vesicle in Bronchopneumonia with Streptococci.

This specimen is from a case of bronchopneumonia complicating a pseudomembranous inflammation of the larynx in scarlatina. Exfoliated epithelium, leucocytes, and a little fibrin with the streptococci form the scanty exudate.

It will thus be seen that while it is convenient to group the exudative forms of pulmonary inflammation on the basis of distinctions which are in part morphological, in part etiological, the types in fact frequently merge or concur. This should not lead to confusion if we remember that these are infectious diseases whose most conspicuous lesion is located in the lungs, and that they are not species in the natural history sense, for which fixed and definite characters must be established, but that the groups only indicate various forms and phases of response of a living organ in various conditions of susceptibility to the damage inflicted by one or another, and not infrequently by two or more combined forms of microorganism. These pneumonias are not considered among the infectious diseases where they logically belong, partly because there are practical advantages in grouping pulmonary lesions together and partly because our knowledge of the relative frequency and significance of the bacterial excitants of the various types is still in many cases too incom-

[1] For a study of the bacteriology of lobular pneumonia, especially in adults, see *Blumer, G.*, Albany Med. Ann., 1901, xxii, 424.

plete to permit the establishment of a distinctive and clearly defined form of infection.[1]

Chemical Pneumonia.

The inhalation of atmospheres rich in oxygen incites, in twenty-four to forty-eight hours, congestion and edema of the lungs with desquamation of the alveolar epithelium, fibrinous exudate into the alveoli, and, finally, a fibrinous pneumonia.[2]

The inhalation of irritating gases, especially chlorine, ammonia, nitrogen tetroxide, bromine, and a large number of the corrosive organic

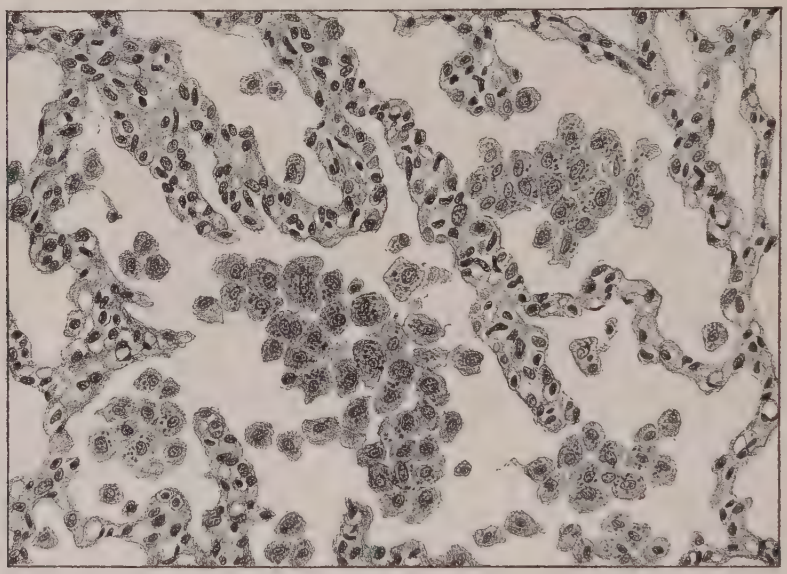


Fig. 428.—Chemical Pneumonia.
Large phagocytic cells with pigment in the alveoli of lung in case of poisoning with nitric oxide.

products now used as destructive agents in war, gives rise to a characteristic type of pneumonia due solely to the chemical action and not necessarily accompanied by bacterial infection,[3] although this may occur.

The inhalation of dilute corrosive vapors may cause no symptoms for six or eight hours, or there may be immediate dyspnea, a feeling of pressure on the chest, cough, cyanosis, and vomiting. These early

[1] For a study of experimental cooling of the body which may induce changes in the blood, predisposing to infection with the pneumococcus, see *Reineboth* and *Kohlhardt*, Deutsch. Arch. f. klin. Med., 1900, lxv, 192. For a study of the effects of cooling in general as a predisponent to infection, see *Lode*, Arch. f. Hyg., 1897, xxviii, 344; also *Kisskalt*, ibid., 1901, xxxix, 142 (bibl.).

For a study of the portals of entry in lung infection, with special reference to the pleura, see *Grober*, Deutsch. Arch. f. klin. Med., 1900, lxviii, 296 (bibl.).

Concerning circulatory changes in the lungs under various pathological conditions, see *Esser*, Centralbl. f. inn. Med., 1901, xxii, 97 (bibl.).

[2] *Karsner, H. T.*, Jour. Exper. Med., 1916, xxii, 149; Jour. Lab. and Clin. Med., 1917, ii, 254.

[3] See, for report of case with experiments on animals and bibl., *Wood, F. C.*, Arch. Int. Med., 1912, x, 478. The best bibl. on nitrogen tetroxide poisoning is contained in *Witthaus* and *Becker*, Medical Jurisprudence and Toxicology, New York, 1911, iv, 301.

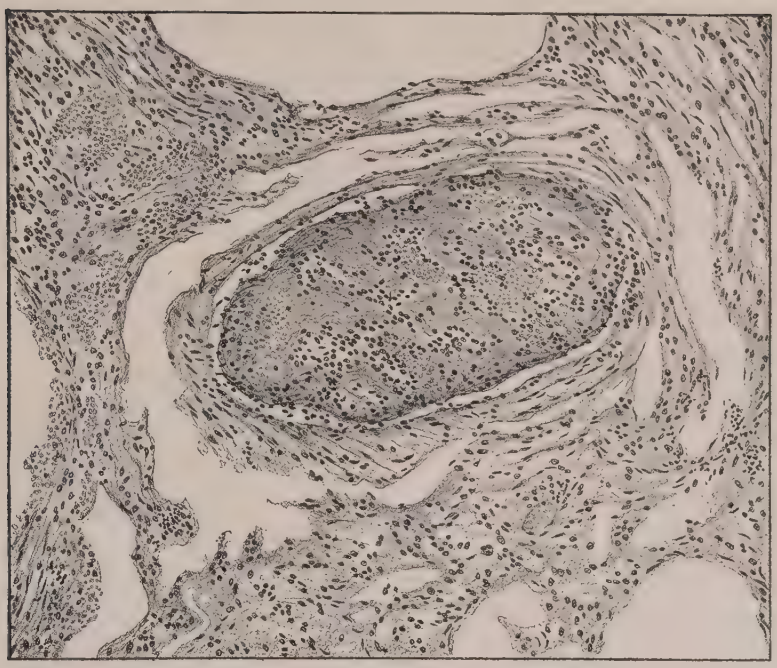


FIG. 429.—CHEMICAL PNEUMONIA.
Thrombus in vessel of lung in case of poisoning with nitric oxide.

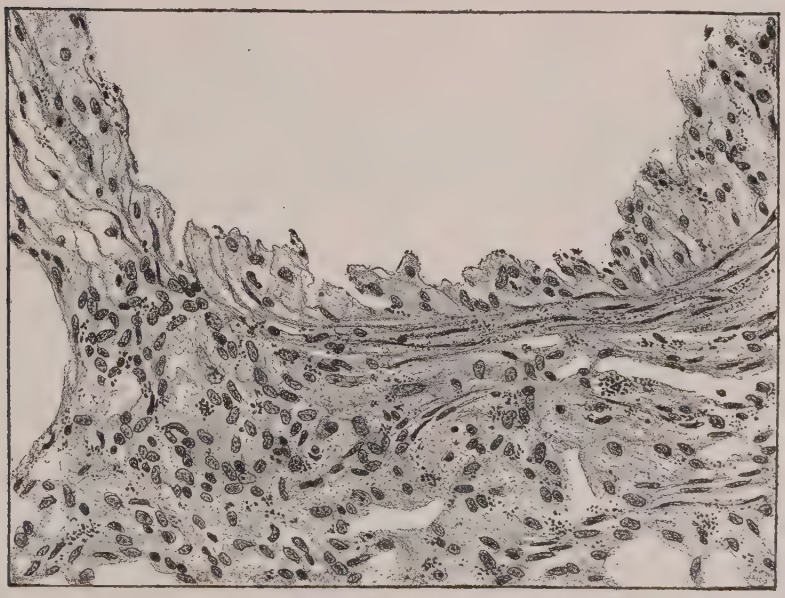


FIG. 430.—CHEMICAL PNEUMONIA.
Wall of bronchus from case of poisoning with nitric oxide, showing loss of surface epithelium and pigmentation of connective tissue.

symptoms occur only when the gas is fairly concentrated. At the end of six to eight hours of comparative comfort, the patient is suddenly attacked with extreme dyspnea and cyanosis; death may occur within forty-eight hours or, rarely, after five to eight days. If the attack is survived, the lungs remain sensitive to infections, and there is usually chronic cough and a tendency to hemoptysis. The sputum is tenacious and of a yellowish or brownish color; in nitrogen tetroxide poisoning this color may be due to staining by the gas itself; in other cases it is due to blood pigment derived from the bronchi or alveoli. At autopsy the larynx, trachea, and bronchi are congested and of a reddish or brownish color; the lungs of those who live for several days are full of emphysema-

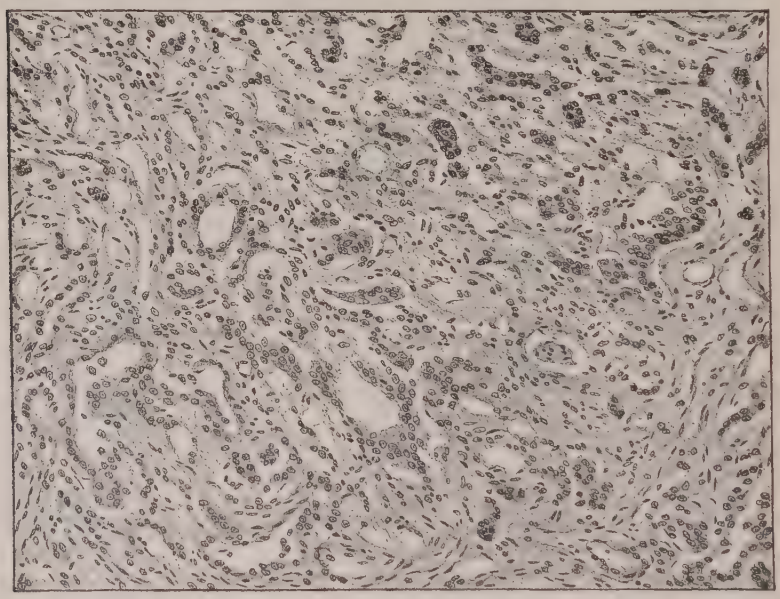


Fig. 431.—Chemical Pneumonia.
Solid portions of lung with remnants of alveolar epithelium in case of poisoning with nitric oxide.

tous areas, and the alveoli contain pigmented cells (Fig. 428). Many of the vessels contain thrombi (Fig. 429); and from the cut surface reddish or brownish fluid exudes. Ecchymoses in the lungs are present in the early stages; there is also an early exudation of fibrin and blood into the alveoli; and the bronchial mucous membrane is almost entirely destroyed (Fig. 430). After a few days, reaction sets in with regeneration of the alveolar epithelium in the form of large blocks or syncytial masses of cells with the growth of new connective tissue in the edematous and collapsed lung (Fig. 431 and 432). The patient may die in this stage. If he survives the bronchial mucous membrane regenerates to a certain extent, but considerable portions of the lung are irreparably damaged by the interstitial inflammation.

Interstitial Pneumonia.

This name is given to a chronic productive inflammation, which involves the connective-tissue framework of the lung and the walls of the air spaces, and results in the formation of new connective tissue and the obliteration of the air spaces (Fig. 433).

Such an interstitial pneumonia may follow acute lobar pneumonia with the production of new intra-alveolar connective tissue, bronchopneumonia, chronic pleurisy, chronic bronchitis, and atelectasis, or may be induced by the inhalation of the dust of coal, stone, or other inorganic substances. Diffuse interstitial pneumonia may occur in syphilis.

The topography of the lesion varies considerably in the different conditions under which the new tissue growth occurs. If it follows acute

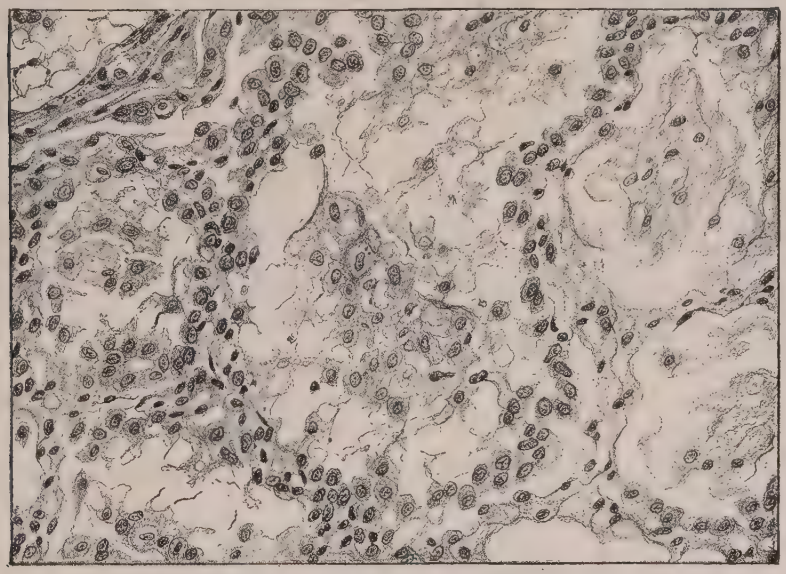


Fig. 432.—Chemical Pneumonia.
Fibrinous and cellular exudate in lung after poisoning with nitric oxide.

lobar pneumonia, one lobe or the whole of one lung may be involved and covered with pleuritic adhesions. The lobe or the lung is small, smooth on section, and firm in texture. The air spaces and small bronchi may be largely obliterated by the new connective tissue. If it follows bronchopneumonia, one or more lobes are studded with fibrous nodules, which correspond to the affected bronchi and the associated lung territory; or a large part of a lobe is converted into dense fibrous tissue; the pleura may be thickened; there may be chronic bronchitis and bronchiectasia. If interstitial pneumonia is associated with thickening of the pleura, bands of connective tissue extend from the pleura into the lung, the bronchi are inflamed and often dilated. When associated with chronic bronchitis there are fibrous nodules around the bronchi, with more or less diffuse connective tissue.

The changes in interstitial pneumonia may occur by a slow hyperplasia of the fibrous tissue or by the formation of granulation tissue, which

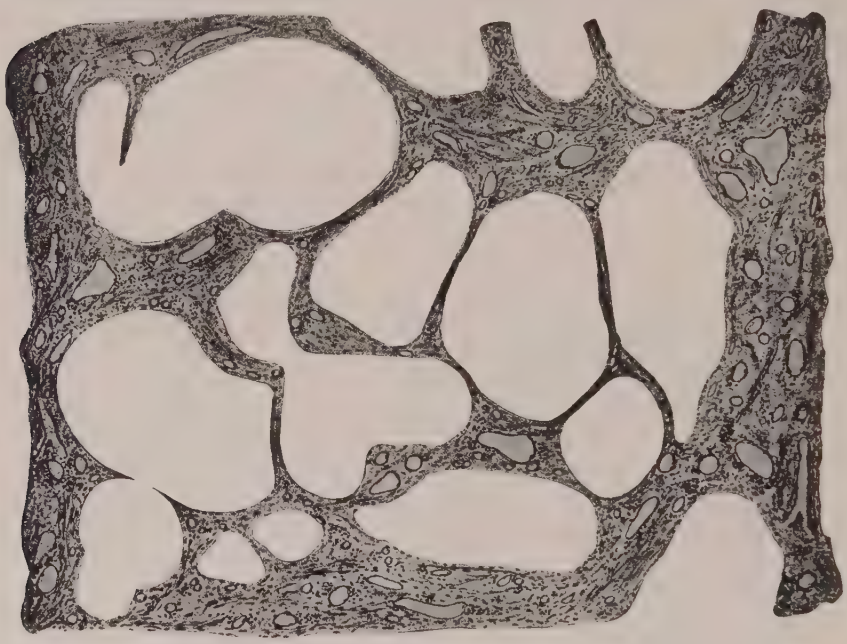


FIG. 433.—INTERSTITIAL PNEUMONIA.
With emphysema. The walls of the enlarged air vesicles and spaces are converted into dense fibrous tissue.

gradually becomes denser with contraction. Although this process is primary in the interstitial tissue, exudates are often present in the air

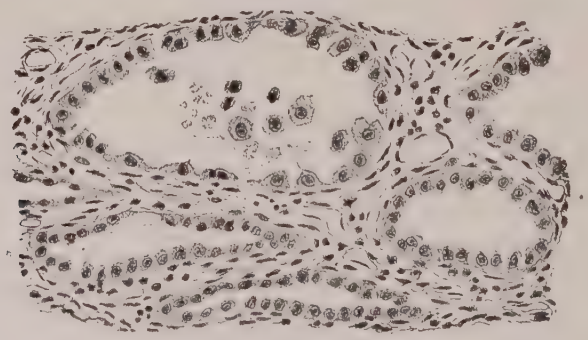


FIG. 434.—CHRONIC INTERSTITIAL PNEUMONIA. REVERSION OF EPITHELIUM IN ISOLATED AIR VESICLES.

spaces; atelectasis may occur, while emphysema and bronchiectasis are common.

Sometimes a noteworthy change occurs in the epithelium lining air vesicles which have been cut off from their neighbors by the new fibrous tissue. The epithelial cells increase in number and become thicker, and finally the small or distorted cavities may be lined with a complete investment of cuboidal cells (Fig. 434). This reversion of the epithelium of the air vesicles to a less differentiated type occurs in many chronic processes in the lungs.

Pigmentation of the Lung.—The inhalation of dust and smoke is so continuous among those who live much indoors that the lungs of nearly all persons from the earliest years are more or less pigmented. The foreign particles which get into the deeper recesses of the lungs are in part taken up by the epithelium of the air spaces, in part are carried by phagocytes or otherwise to the interstitial tissue of the lungs (Fig. 435). Here, either within cells or without, they are deposited along and within the lymph-channels or in the lymph-nodules of the pleura and interstitial

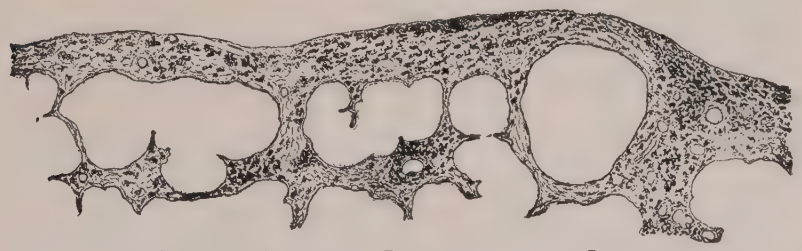


FIG. 435.—ANTHRACOTIC PIGMENTATION OF THE LUNG.
Showing pigment beneath the thickened pleura and in the thickened septa of the emphysematous lung.

tissue (Fig. 436), or they may be carried to the lymph-nodes at the root of the lungs. Rarely, this inhaled dust passes the tracheal and bronchial lymph-nodes and may be deposited in the viscera, especially in the liver and spleen.

Under ordinary conditions a moderate deposit of inhaled pigment particles in the lungs does not seem to be of great significance, but it does lead, if present in amounts as large as are frequently found in the air of many private houses, stores, factories, theaters, and other places of public assembly, to obliteration of lymph-channels and conversion of lymph-nodes into masses of pigmented fibrous tissue; and there is little doubt that in this way it may predispose to more serious lesions.[1] On the other hand, miners and others working or confined in smoky air, stone or metal workers, and the like, are liable to excessive pigmentation and to develop interstitial pneumonia, especially marked at first along the interlobular septa and frequently associated with chronic bronchitis, emphysema, atelectasis, or bronchiectasia. This condition of the lung when due to the inhalation of coal dust is called *anthracosis;* when due to dust of various minerals, *chalicosis;* when due to iron dust, *siderosis.*[2]

[1] For a study of the significance of pulmonary anthracosis, see *Haythorn, S. R.*, Jour. Med. Research, 1913, N. S. xxiv, 259.

[2] For a study of the condition of iron pigment in cells and tissues see *Arnold, J.*, Virchows Arch., 1900, clxi, 284.

The general process has been called *pneumokoniosis*. The color varies in these lungs with the character and amount of the deposited material, which is frequently quite unevenly distributed, though usually there is more in the upper than in the lower lobes. The amount of foreign material in such lungs is sometimes large,[1] but in the normal urban dweller it amounts to only a few milligrams.[2]

Tuberculous Pneumonia.

General Considerations.—Tuberculous inflammation of the lungs is similar in nature to tuberculous inflammation in other parts of the body.[3] But since the morphological features of the response of a tissue to injury are largely dependent upon the form and capacities of its cells, it is not surprising that in such complex organs as the lungs, the lesions of tuberculosis should present many variations from the usual type elsewhere. The bronchial passages and the connecting air spaces, the numerous blood- and lymph-channels, especially favor the distribution of the tubercle bacillus within these organs; the open texture of the lungs permits, as in other forms of pneumonia, of great accumulation of exudate, while the delicacy and thinness of the air chambers favor extensive disintegration of the old or new-formed tissues or exudates when these have become necrotic under the influence of the poisons of the tubercle bacilli.

Thus the variety of cells and tissues involved and their peculiar relationships to one another and to the invading organisms render the lesions of pulmonary tuberculosis more complex in morphology than are tuberculous lesions in any other part of the body.

The classification of these lesions is largely based upon topographic considerations and is not to be regarded as indicating fundamental differences in the reaction of the tissues.

Portals of Entry.—Tubercle bacilli may enter the lungs through the blood- and lymph-vessels, being brought from a focus of tuberculous inflammation in another part of the body, or, as is frequently the case, may be introduced through the air passages by the inhalation of floating dust particles, among which are living tubercle bacilli. There is evidence that tubercle bacilli may enter the body through the nasal and buccal mucosa or the tonsils or through the gastrointestinal mucous membrane without the development of tuberculous lesions at the point of entry.[4]

Reaction of Tissue.—The introduction of tubercle bacilli into the lungs may induce an exudative inflammation with the accumulation of fibrin, leucocytes, and exfoliated epithelium in the air spaces; a productive inflammation with the growth of epithelial cells, or of round-cell tissue, or of a tissue composed of basement substance, large and small

[1] For a study of the lungs in extreme anthracosis see *Hodenpyl, E.*, Proc. New York Path. Soc., 1899, p, 79. For a summary of the protective mechanism of the respiratory passages see p. 684. For summary of dusty trades and consumption, see *Hoffman*, Bureau of Labor, Dept. of Commerce and Labor, U. S. A., Bull. 79, 1908, and Bull. 82, 1909 (bibl.).

[2] *Boer*, Arch. f. Hyg., 1911, lxxiv, 73.

[3] A complete review of the subject of pulmonary tuberculosis will be found in *Bauer, Schröder*, and *Blumenfeld*, Handbuch d. Tuberkulose, Leipzig, 1914.

[4] For a discussion of the sources and portals of entry of the tubercle bacillus, see p. 303.

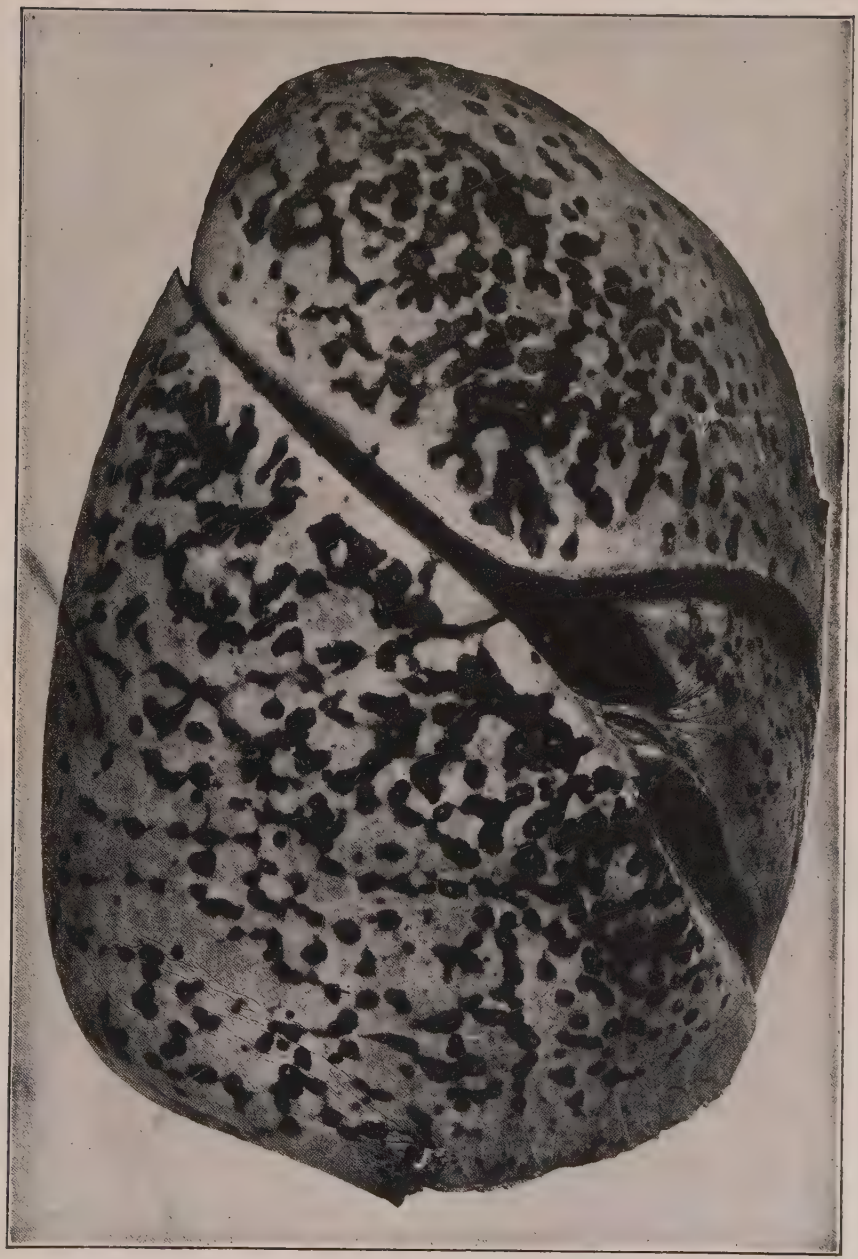


FIG. 436.—ANTHRACOSIS OF THE LUNG.

A few tubercles are seen at the centers of the pigmented areas. There are slight pleuritic adhesions between the lobes. This is from a photograph of the lung of an actor who had been for many years upon the stage in the nearly always dusty air of theaters.

cells, and giant cells, called tubercle tissue (see page 288); or there may be added necrosis of the new tissue and of portions of the lung. All of these phases of tuberculous lesions may and usually do occur together.

The character of the inflammation in each case seems to be governed by the type of cells especially involved, by the number, virulence, and proliferative capacity of bacilli which are introduced into the lungs, and the way in which these enter, as well as by the susceptibility of the individual. If a large number of virulent tubercle bacilli are inhaled or aspirated through the bronchi, or if the bacilli grow with great rapidity, both productive and exudative inflammations may be set up in a considerable portion of the lungs. If, on the other hand, but few bacilli enter and their proliferation or virulence is not extreme, or if these find their way in small numbers into the lungs through the blood-vessels or lymphatics, then there may be small foci of productive inflammation with but little exudation. The tuberculous alterations in the lungs are usually accompanied or followed by a series of secondary processes which often complicate the condition of the patient as well as the morphological appearances of the organs. The obliteration or destruction of the smaller blood-vessels of the lungs in the tuberculous areas contributes to the gray or whitish appearance of the lesions, due largely to new-formed tissue or accumulated exudate. The formation of fibrous tissue in the attempts at repair of the damage wrought by the tubercle bacillus often dominates the structural picture.

Classifications.—The traditional distinctions between acute and chronic forms of pulmonary tuberculosis are often morphologically not at all well defined and are of value chiefly for clinical purposes.

It has been customary to set apart those forms of acute tuberculosis of the lungs in which the lesions are in the form of small discrete so-called "miliary" foci, calling the condition *Acute Miliary Tuberculosis.* The other tuberculous lesions involving in varying degree the lungs and the bronchi with associated and often extensive exudative, necrotic, and reparative processes have been commonly jumbled together as *Acute* and *Chronic Phthisis,* many phases of which have been elaborately described as if they were the expression of independent processes.

With our present knowledge of the nature and etiology of tuberculosis it seems better, however, to review the lesions of pulmonary tuberculosis under the following primary headings:

1. Focal or miliary tuberculosis.
2. Tuberculous bronchopneumonia.
3. Complex forms of nodular and diffuse tuberculous lesions.
4. The formation of cavities.
5. Secondary lesions in pulmonary tuberculosis.
6. Concurrent infection.

Focal Tuberculosis. (*Miliary Tuberculosis*).

Acute Miliary Tuberculosis.—The rapid and widespread development of miliary tubercles in the lungs is often a part of general tuberculosis,

although the lesion may be most extensive in the lungs. Both lungs are apt to be involved, but the distribution, number, size, and character of the miliary tubercles differ in different cases. The tubercles are found in the parenchyma of the lung, in the connective tissue forming the septa, along and in the walls of the bronchi and blood-vessels, and in the pulmonary pleura. They may be scattered singly through the lungs (Plate VI), or aggregated in groups (Plate VIII and IX). They may be separated by considerable interspaces, or so close together that the lung is rendered nearly solid. Some are so small and transparent that they can hardly be seen with the naked eye; others are larger and more opaque and may have a lighter center marking the area of necrosis.

In many cases it is evident that the lungs are infected through the blood-vessels or the lymphatics, for the general tuberculous infection

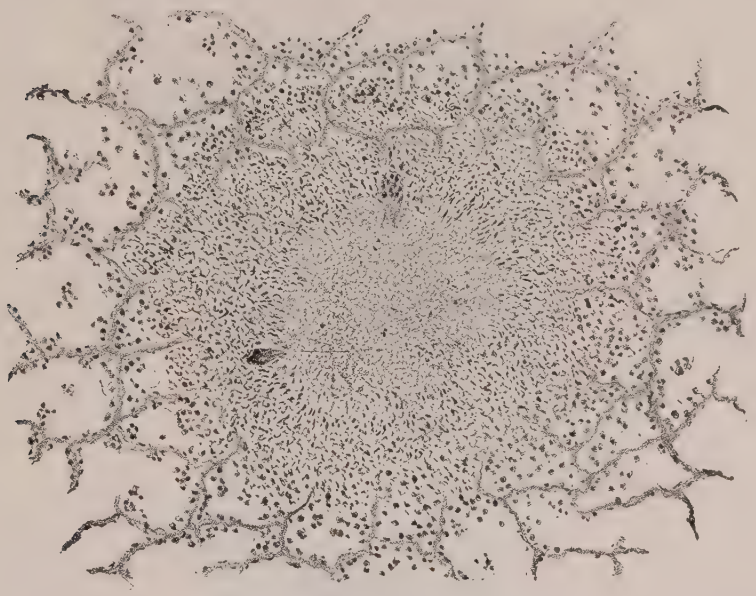


FIG. 437.—MILIARY TUBERCLE OF LUNG.

This tubercle has replaced several air vesicles whose walls are obliterated. In the center is an area of coagulation necrosis; outside of this is a zone of organized tubercle tissue; the surrounding air vesicles contain a cellular exudate.

is secondary to a localized tuberculosis either in the lungs or in some other part of the body. In a considerable proportion of cases of miliary tuberculosis of the lungs, tuberculous lesions of the bronchial lymph-nodes or of the lung tissue at the apex of much longer standing indicate the probable immediate source of origin of the widely distributed tubercle bacilli. Very often in miliary tuberculosis of the lungs the tubercles in one part of the lungs are larger and appear to be older than those in other parts. Thus it is not infrequent to find the tubercles in the upper portion of the lungs more abundant, larger, and more fibrous than in the lower lobes (see Plate IX). It is in fact probable that in many cases

of acute miliary tuberculosis of the lung, either associated or not with older local tuberculous lesions from which the distribution of bacilli may have taken place, the generalization has occurred, not at once, but by successive fresh infections.[1]

Miliary tubercles in the lungs are in structure essentially similar to those formed elsewhere in the body, except that the filling of the air spaces with exudate makes the lesion somewhat more complex.

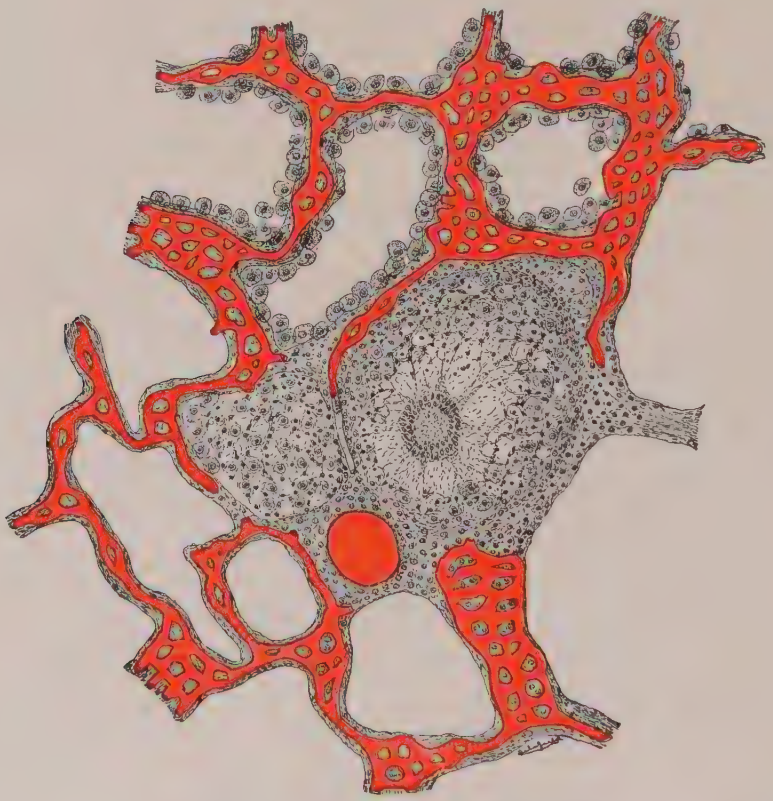


FIG. 438.—A MILIARY TUBERCLE OF THE LUNG.

Involving only two air vesicles, of which the walls are infiltrated and the cavities filled with tubercle tissue. The blood-vessels of the air vesicles are injected, except where these are obliterated by the tuberculous involvement of their walls.

The tubercles may be composed of small spheroidal cells or of larger polyhedral cells with more or less fibrous stroma, or of small and large cells and stroma. Giant cells may be present, coagulation necrosis is usual (Fig. 157, page 292). Such forms of miliary tubercles may be and commonly are associated with the presence of an exudate in the adjacent or involved air vesicles (Fig. 437). This exudate may be largely made up of exfoliated epithelial cells which have proliferated; or with these there may be serum, leucocytes, and fibrin. The blood-vessels within

[1] For references to the origin of miliary tuberculosis see *Benda, C.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 447; see also *Ribbert, H.*, Deutsch. med. Wchnschr., 1906, xxxii, 5.

Miliary Tuberculosis (Acute) of the Lung.

The miliary tubercles, small and irregular in shape, are distributed throughout the lung—more abundantly in the upper and middle thirds.

The blood-vessels are injected with blue gelatin, so that in this photographic reproduction of the specimen the uninvolved portions of the lung are dark, while the tubercles—in which the blood-vessels are compressed or obliterated—are light.

the tubercles which replace the lung tissue are partially or wholly obliterated (Fig. 438).

But the miliary foci of tuberculous inflammation in the lungs may consist wholly of inflammatory exudate which early becomes necrotic, often with necrosis of the walls of the involved air spaces. Such tubercles of the exudative type are apt to occur in children and usually contain large numbers of tubercle bacilli. They may occur in connection with various other phases of acute and chronic pulmonary tuberculosis.

When miliary tubercles are situated in the parenchyma of the lung the walls of the air spaces may be visible in the new growth or they may be largely or wholly obliterated (Fig. 439).

In the obliteration of the walls of the air vesicles, their former situation may be indicated by structureless bands or streaks of necrotic material, or they may disappear altogether.

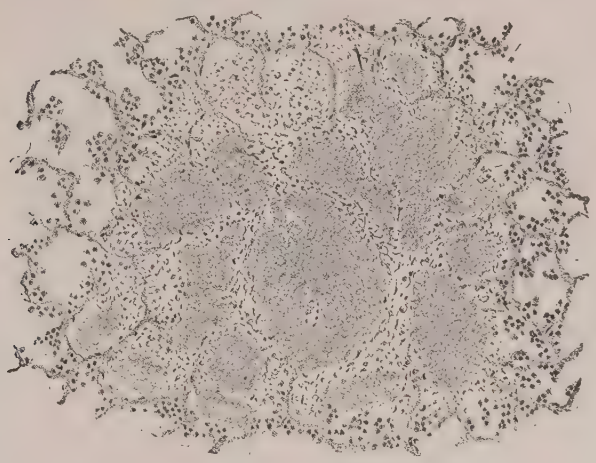


FIG. 439.—A MILIARY TUBERCLE OF THE LUNG.

This tubercle is largely caseous, the walls of the involved air vesicles being merely indicated in the dead mass by slightly stained streaks or bands. There is cellular exudate in the surrounding air vesicles.

Chronic and "Healed" Miliary Tubercles.—The small foci of tuberculous inflammation which are called miliary tubercles may, as we shall see later, extend and coalesce so that with more or less exudative pneumonia large areas of the lung may become consolidated, thus developing one of the forms of pulmonary tuberculosis called phthisis.

On the other hand, small tuberculous foci in the lungs may with or without extensive necrosis become surrounded by or converted into masses of dense fibrous tissue. These fibrous-tissue masses, which are often called "healed tubercles" (Fig. 440 and 441), may contain necrotic material, are often mottled black from anthracotic pigment, or they may be calcified at the center. Tubercle bacilli may be absent from them, or the bacilli may remain alive within them for a long time quiescent but still virulent. When such circumscribed masses of more or less fibrous tubercle tissue are scattered through the lungs, although the individual

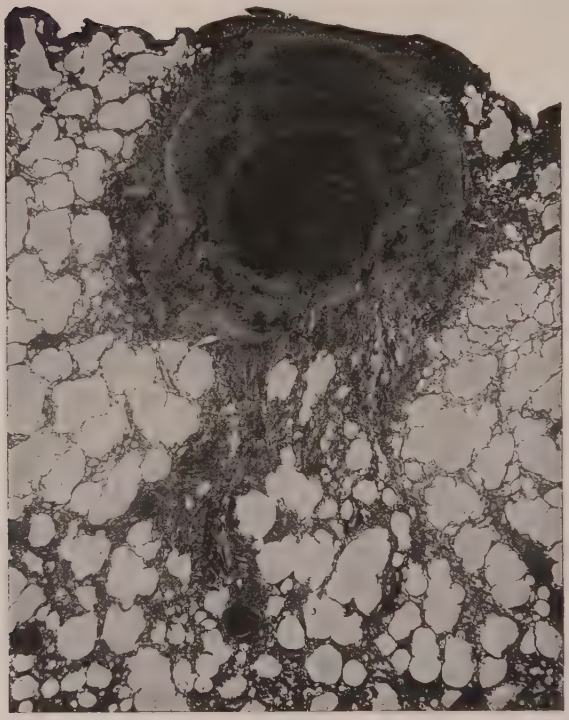


FIG. 440.—AN OLD FIBROUS TUBERCLE OF THE LUNG—"HEALED TUBERCLE."

The central portion is necrotic and irregularly pigmented. The periphery is composed of dense pigmented fibrous tissue. There are emphysema and distortion from cicatricial contraction of the fibrous tissue.

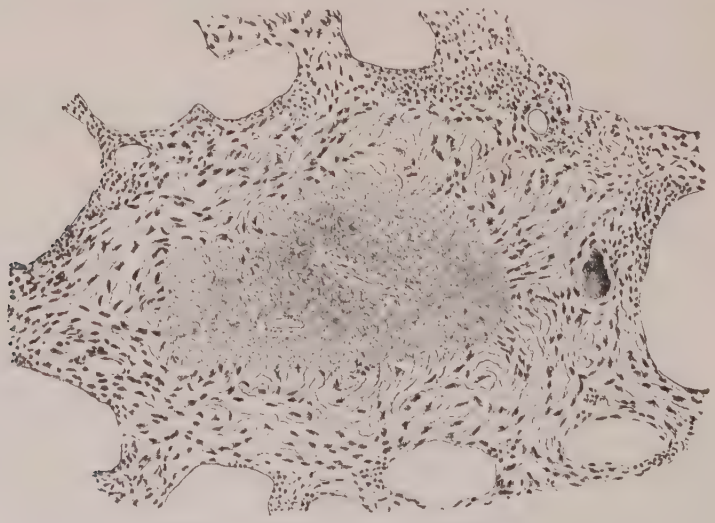


FIG. 441.—A FIBROUS TUBERCLE—"HEALED TUBERCLE" OF THE LUNG.

The center is caseous, the fibrous tissue surrounding this is dense, the walls of the surrounding air spaces are thickened. A giant cell at the right is calcified.

masses may be of considerable size, the process is sometimes called "*chronic miliary tuberculosis.*"

It should be remembered that the new fibrous tissue which forms in and about miliary tubercles, as well as other tuberculous lesions, is the result of a distinctly reparative process in which the already formed tubercle tissue or its products apparently act somewhat as foreign bodies may in inducing fibrous-tissue growth.

Tuberculous Bronchopneumonia.

In another most important phase of tuberculous inflammation of the lung there is an involvement of the walls of the smaller bronchi and the

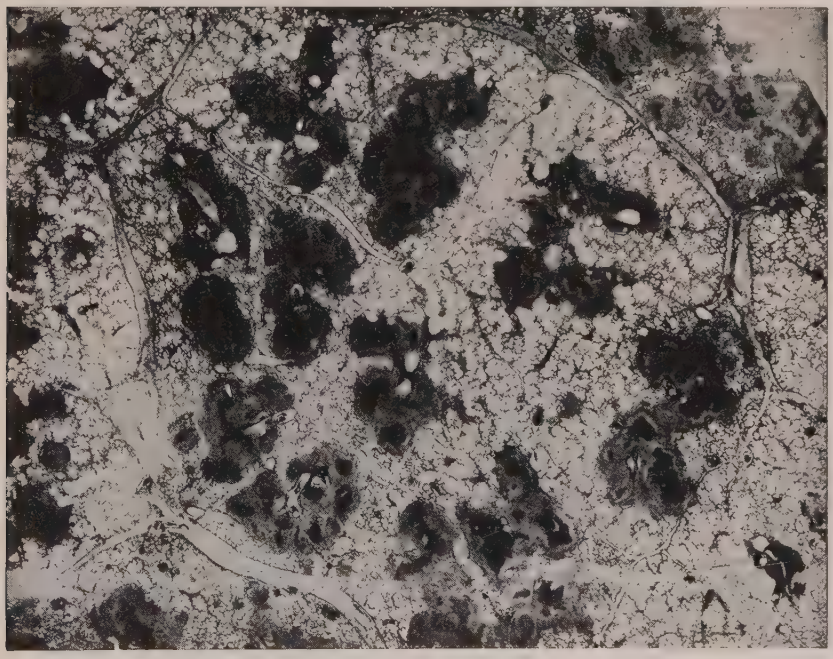


Fig. 442.—Tuberculous Inflammation of the Lung with Cheesy Degeneration about the Bronchi in a Single Lobule of the Lung—Tuberculous Bronchopneumonia.

associated groups of air spaces. This may occur through inhalation of bacilli or by their aspiration from an established tuberculous focus; for example, from a lesion at the apex, or, as is often the case in children, from tuberculous bronchial lymph-nodes; or infection may take place through the blood- or lymph-vessels. In the early stages of tuberculous bronchopneumonia the cut surface of the fresh lung may present small gray or yellowish white areas of consolidation with necrosis clustered about the small or terminal bronchi (Plate VII). The process is at first largely exudative, involving a catarrhal and necrotic inflammation of the mucous membrane of the bronchus with more or less exudate—which also may soon become necrotic—in the associated groups of air spaces (Fig. 442). Sometimes organized tubercle tissue may form in the walls of

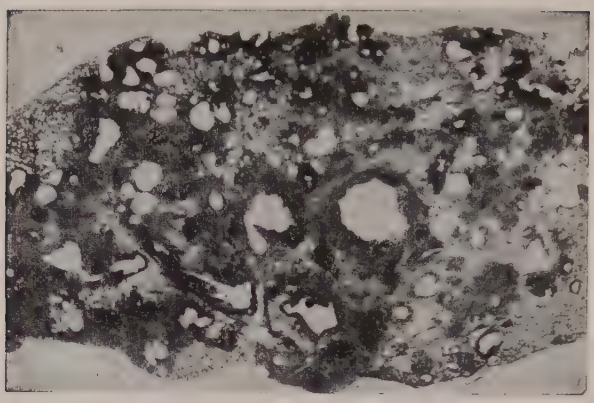


FIG. 443.—TUBERCULOUS BRONCHOPNEUMONIA.

The walls of the bronchi are thickened and caseous and are surrounded by zones of exudative and caseous pneumonia. This cut shows a small region, more highly magnified, of a lesion similar to that shown in Plate VII.

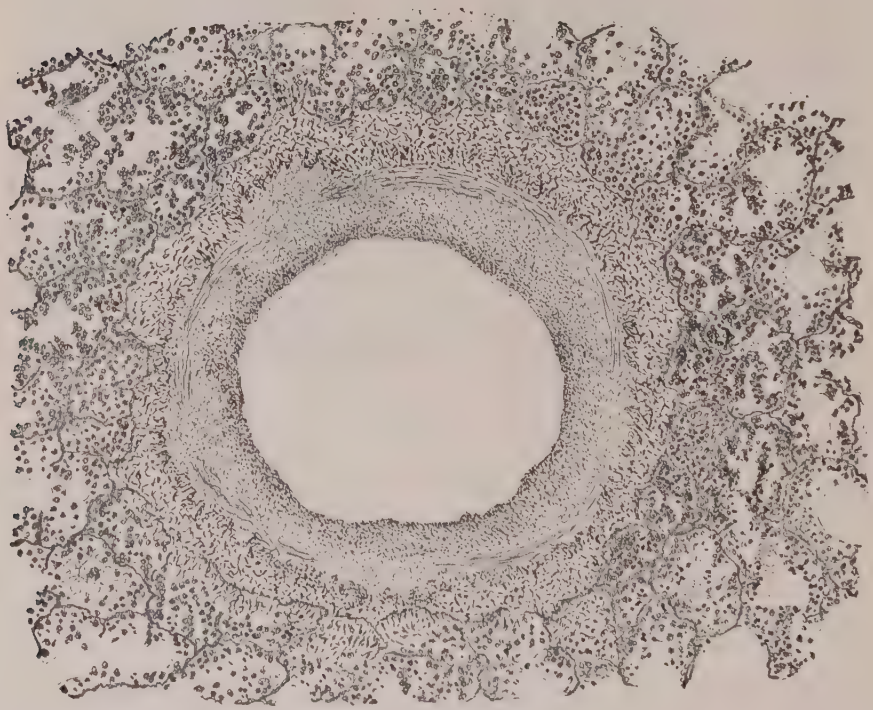


FIG. 444.—TUBERCULOUS BRONCHOPNEUMONIA.

The wall of this medium-sized bronchus is caseous, tubercle tissue is formed about it and is extending into the surrounding lung tissue. A cellular exudate is seen in the contiguous air vesicles.

Tuberculous Broncho-Pneumonia.

The walls of the smaller bronchi are involved, being thickened and caseous, while the ulceration of many of them has led to the formation of numerous small cavities.

The blood-vessels are injected with blue gelatin, so that the less affected and the intact parts of the lungs are the darker.

the bronchi, with thickening of the walls and obliteration of the blood-vessels of the adjacent air spaces.

By the extension of the process from one and another affected bronchus, and the coalescence of these, large areas of the lungs may become involved. In this more advanced stage of bronchopneumonia the larger and smaller consolidated areas may be dark red with firmer gray or yellowish gray central portions, in which the blood-vessels are obliterated, or the whole area may be solid and in the fresh lung grayish white. This new-formed tissue may undergo necrosis and ulceration so that with an advancing consolidation of the lung tissue about the bronchi numerous

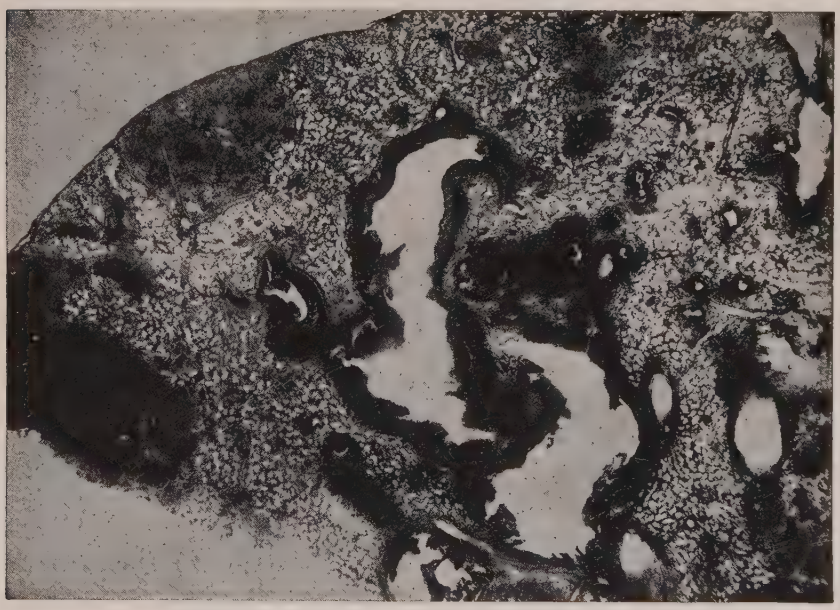


FIG. 445.—TUBERCULOUS BRONCHOPNEUMONIA.

Showing the formation of cavities in the lung in acute phthisis. To the right are small, in the center large, tuberculous bronchiectatic cavities. At the left are areas of tuberculous consolidation with caseation in their central portions.

larger and smaller, rough, irregular cavities may be formed (Fig. 443). The walls of the larger bronchi also may become the seat of a tuberculous inflammation with more or less necrosis (Fig. 444). Ulceration of these necrotic bronchial walls may lead to the formation of ragged cavities (Plate XI and Fig. 445).

The secondary development of dense fibrous tissue in connection with tuberculous bronchopneumonia is a marked feature of the persistent or chronic forms. Tuberculous bronchopneumonia is one of the most important of that complex of pulmonary lesions called phthisis, and is commonly associated with other forms of tuberculous involvement of the organ—miliary tubercles, larger areas of consolidation, etc.

Complex Forms of Nodular and Diffuse Tuberculous Lesions.

With or without the various well-defined forms of tuberculous bronchopneumonia and miliary tubercles above described, there may be more or less circumscribed small or large areas of productive and exudative tuberculous inflammation of the lung with necrosis, both of the lung tissue, the new-formed tissue, and the exudate (Plate XIV). These may develop as the result of fresh infections of the lung through the lymphatics or otherwise. These areas or nodules may coalesce so that whole lobes or parts of lobes of the lungs may become consolidated (Plates IX and X). Microscopically, these consolidated areas may be composed of tubercle tissue more or less necrotic, with partial or total obliteration of the walls of the air spaces. On the other hand, when the process has been exudative as well as productive in character, one may see in the solid areas the outlines of the air vesicles and larger spaces; but these, together with the inclosed exudate, may be necrotic and granular with few stained nuclei and fragments of chromatin. Much of the exudate which fills the air vesicles either within or about these more densely consolidated areas may not be caseous or necrotic, but may consist of well-preserved or fatty epithelial cells, or of these with varying quantities of leucocytes and fibrin.

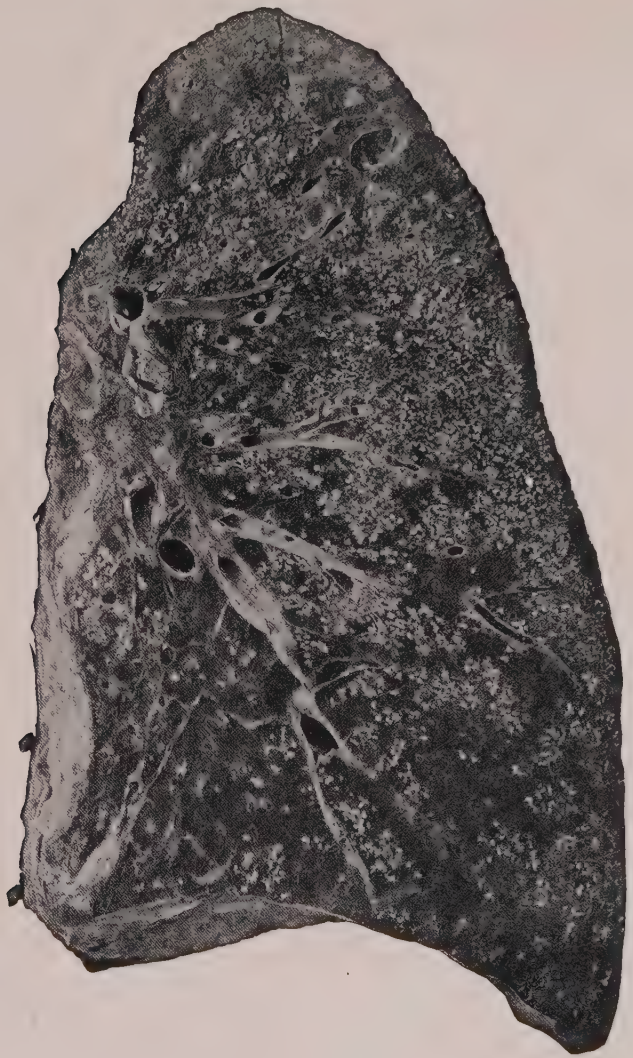
Aside from these complex forms of nodular and diffuse tuberculous lesions one may recognize a **Diffuse Exudative Tuberculous Inflammation of the Lungs of Acute and of Chronic Type.—Cheesy Pneumonia; Pneumonic Phthisis.**

1. Acute Type.—Sometimes large areas or whole lobes or the whole lung may be the seat of an exudative process by which the affected region becomes solidified, the exudate consisting of epithelium with more or less fibrin and pus. This exudate, together with the lung tissue, soon undergoes necrosis, so that the solidified lung becomes dense, mottled, and gray in color. Extensive disintegration (Fig. 446) of the consolidated and necrotic portions of the lung may take place, with the formation of large ragged cavities (see Plate XII). In many cases enormous numbers of tubercle bacilli are present in the exudate of the involved region in this type of exudative and necrotic pulmonary tuberculosis.

2. Chronic Type.—There may be a more gradual development of the exudate, involving larger or smaller areas, often with tuberculous thickening and necrosis of the walls of the air spaces. With this as with other forms of pulmonary tuberculosis there may be associated a growth of simple fibrous tissue with the formation of cavities.

Not infrequently the exudate in such forms of diffuse tuberculous inflammation of the lung is less cellular and more serous or serofibrinous in character, when the appearance of the consolidated region is translucent and gelatinous.

Obliteration of the larger blood-vessels by thrombosis or inflammation of the wall often plays an important part in most forms of tuberculous lesions of the lungs. When large trunks are involved, extensive lung



Peribronchial Tuberculosis with Diffuse (Chronic) Tuberculous Lesions in the Apex.

There is in the apex tuberculous consolidation with coagulation necrosis (caseation), new fibrous tissue, and a small cavity. The middle third of the lung contains many small single and clustered miliary tubercles and foci of tuberculous peribronchial lesions. The lower third contains a few similar small tuberculous foci, also scattered and in clusters.

The appearance of the lung leads to the conjecture that tubercle bacilli may have been gradually disseminated from the earlier lesion in the apex. The blood-vessels are injected with blue.

areas, supplied by the occluded vessels, particularly those in which exudate is present, may become necrotic *en masse*, then often appearing on section smooth, shining, grayish-white in color, and bloodless.

FIG. 446.—ACUTE PULMONARY TUBERCULOSIS—EXUDATIVE TYPE (ACUTE PHTHISIS—CHEESY PNEUMONIA); WITH EXTENSIVE DISINTEGRATION AND FORMATION OF CAVITIES.
The pleura is much thickened.

THE FORMATION OF CAVITIES IN PULMONARY TUBERCULOSIS.

We have seen that in tuberculous bronchopneumonia ragged cavities may form by a progressive necrosis and disintegration of the thickened walls of the affected bronchi and the adjacent lung tissue (Plate XI

and Fig. 445). Similar destructive alterations may occur in the areas of tuberculous and necrotic tissue which involve larger and smaller portions of whole lobes (Plate XIII). This is most often rapid and extensive in solidified and necrotic areas of the exudative type (Plate XII and Fig. 446). These ragged cavities may communicate with one another as well as with the bronchi.

Fig. 447.—Chronic Pulmonary Tuberculosis (Chronic Phthisis), with Cavities.

There is much dense fibrous tissue in the upper lobe surrounding and between the cavities, as well as in the upper portion of the lower lobe.

While at first without distinct limiting walls, if the necrotic process be not too active and extensive, new fibrous tissue may gradually form about tuberculous cavities (Plate XIV, and Fig. 447); and these may become lined with granulation tissue or a layer of new-formed tubercle tissue. Here an enormous proliferation of tubercle bacilli may occur for long periods. These may be cast out in the sputum or aspirated into other parts of the lungs. The old blood-vessels of the involved portion of the lung may lie upon the walls or stretch across these cavities, sometimes with obliterated lumina, sometimes still permeable; and from these hemorrhages may occur. There may be continuous and prolonged suppuration of the walls of the cavities and putrefactive processes may be incited by the advent through the air passages of various forms of bacteria. The walls of cavities may become fibrous with an arrest of the tuberculous process, and they may be shut off from bronchial communication.

Secondary Lesions in Pulmonary Tuberculosis.

A variety of secondary processes may be associated with the various phases of pulmonary tuberculosis which we have briefly reviewed. The *blood-vessels* in affected regions may be intact, or, as we have seen, their walls may be involved in the productive and necrotic processes, with thrombosis or obliteration of the lumen; or more or less extensive hemor-

Diffuse and Focal (Chronic) Pulmonary Tuberculosis—"Chronic Phthisis."

In the upper third of the lung there is tuberculous broncho-pneumonia with commencing ulceration of small bronchi: nearly complete consolidation from the extension and coalescence of small tuberculous foci and diffuse formation of fibrous tissue.

In the lower third of the lung are irregular, dense, sharply outlined tuberculous foci (chronic miliary tubercles).

In the middle third there is tuberculous pneumonia of the exudative type, the incompletely consolidated areas having become, in part, caseous.

The less involved portions of the lung in this, as in the other injected specimens, are the darker.

rhages may occur. If the consolidation be not complete, lung tissue, often in a condition of *atelectasis* or *emphysema* and with more or less cellular or granular exudate, may remain between the tuberculous areas. Miliary tubercles may be scattered among the larger consolidated masses or in parts of the lung otherwise free.

In chronic forms of pulmonary tuberculosis the anthracotic *pigment* is often conspicuous, particularly in the cheesy and fibrous areas, standing out in masses and streaks in contrast to the new or dead tissue. Furthermore, there may be associated with the lung lesions acute exudative or chronic fibrous *pleuritis* with adhesions; *tuberculous pleuritis* of varying extent; *empyema;* and *pneumothorax.* There is nearly always more or less chronic *catarrhal bronchitis* or *bronchopneumonia* and frequently *bronchiectasia.*

Tuberculous inflammation in the bronchial lymph-nodes frequently accompanies and often precedes the development of pulmonary tuberculosis. In children the tuberculous lymph-nodes often extend far into the lung and may on softening give rise to cavities at a considerable distance from the hilus of the lung.

Tuberculosis in other parts of the body is common in connection with pulmonary tuberculosis.

In all these various processes new-formed *fibrous tissue,* not tuberculous in character, may develop, variously distorting the lungs and sometimes inclosing the tuberculous areas. There is much reason for the belief that the characteristic tubercle-tissue formation in all phases of tuberculosis is a response of the living cells to injury, which as in other types of inflammation is fundamentally conservative (see page 127). But whether this be so or not, it is certain that it is through the development of fibrous tissue, which is so important a feature in persistent phases of pulmonary tuberculosis, that the delimitation or replacement of tuberculous foci, the encapsulation of tuberculous cavities, etc., occur. While, therefore, fibrous-tissue formation in the lung is frequently associated with the necrotic and other destructive tuberculous lesions, and is often a very conspicuous factor, it should be remembered that the healing which takes place in the majority of cases in man after moderate infection is achieved through its agency.

It is especially upon the presence or absence of fibrous tissue in the lesions that the distinction between acute and chronic phthisis is based.

It will be seen from this brief outline of various prominent phases of pulmonary tuberculosis that the gross appearances of the lungs are most diverse, although the processes by which these changes are induced are few and comparatively simple. While no two lungs are quite similar in the complex phases of the lesion, systematic gross and microscopical examinations soon enable the student to recognize the type of lesion under great complexity of detail.

The Distribution of the Lesions in Pulmonary Tuberculosis.

Aside from general miliary tuberculosis in which the tubercles are widely distributed throughout one or both lungs, the most common seat

and starting-point of tuberculous lesions in adults is the apical region or the depth of the lung, particularly the right, somewhat below the apex.[1] In children, the tuberculous process more frequently commences in the bronchial lymph-nodes (Plates V and XIII).

From the apex the tuberculous process may extend downward, and with various forms of lesions involve more or less of the lungs. It is common to find at autopsies older fibrous lesions about the apices while marks of more active processes are to be seen below (Plate XIV). In a considerable percentage of bodies examined at autopsies, small and often healed tuberculous foci are found at the apex or in the bronchial lymph-nodes without evidence of extension of the process.

Concurrent Infection in Pulmonary Tuberculosis.

While it has been definitely established that tubercle bacilli are the excitants of both the productive and the exudative forms of tuberculous inflammation, these bacilli are not infrequently associated in pulmonary tuberculosis with other organisms, especially with the Streptococcus and Staphylococcus pyogenes, with Diplococcus pneumoniæ, and with the influenza bacillus.

There is reason to believe that in many cases at least the concurrent infection of tuberculous lungs with the Streptococcus pyogenes may be an important factor in the formation of cavities in areas of consolidation already established.[2] The pyogenic cocci apparently play an important part in the bronchitis which so often accompanies acute and chronic phthisis.

Bacteriemia has been shown to exist in a certain proportion of cases of active progressive pulmonary tuberculosis, but in many such cases the blood is sterile.[3]

Artificial Pulmonary Tuberculosis in Animals.

Much light may be gained upon the successive steps in the development of the lesions of pulmonary tuberculosis as well as upon the rapidity with which in a susceptible animal the lesion may develop, by the study of the tuberculosis artificially induced in rabbits with pure cultures.

By the injection of tubercle bacilli alone and associated with streptococci into the lungs of rabbits through the trachea, it has been possible to reproduce very closely the lesions of pulmonary tuberculosis in man.[4]

If a small quantity of a pure culture of the tubercle bacillus in very minute flocculi be mixed with a considerable quantity of salt solution and introduced into the lungs of rabbits through the trachea, a number of small areas of consolidation are produced which have the gross appearance of miliary tubercles (Fig. 448). These small areas of consolidation are composed of epithelial cells and leucocytes. After the development of these cell masses, which may occur within a few hours, they may remain with little apparent change, or become more or less infiltrated with leucocytes, or become cheesy,

[1] For a suggestive consideration of apical vulnerability, see *Hutchinson*, Studies in Human and Comparative Pathology, 1901, p. 81.

[2] For bibliography of concurrent infection in tuberculosis, see *Avery* and *Lyall*, Jour. Med. Research, 1913, N. S. xxiii, 111; *Pettit*, Jour. Infect. Dis., 1911, ix, 237; also *Prudden*, New York Med. Jour., 1894, lx, 1.

[3] For a study of bacteriemia in pulmonary tuberculosis, see *Jochmann*, Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 558.

[4] *Prudden*, New York Med. Jour., 1894, lx, 1.

Diffuse (Chronic) Pulmonary Tuberculosis—"Chronic Phthisis."

In the upper half of the lung there are scattered miliary tubercles and irregular areas of consolidation, with a diffuse formation of fibrous tissue; the pleura is thickened. A large portion of the lower lobe is densely consolidated from tubercle tissue and exudate with coagulation necrosis of the involved regions. These regions are light in color, dense, hard, and bloodless. Such dead caseous areas may persist for some time, or may soften and disintegrate, giving rise to cavities.

Tuberculous Bronchiectatic Cavities in Pulmonary Tuberculosis.

The advancing tuberculous involvement of the walls of the larger bronchi in the upper lobe is associated with ulceration, so that the bronchiectatic cavities gradually become larger. In the upper portion of the upper lobe there is diffuse consolidation with caseation: the lower portion of the lobe shows miliary tubercles and partial consolidation of the lung about them by exudate.

The lower lobe is free save for a few scattered tubercles. The blood-vessels are injected with blue so that the uninvolved portions of the lung are dark.

or be surrounded by a dense zone of small spheroidal cells; or small foci of new tissue with more or less exudate, and necrosis, may form.

When larger quantities of the tubercle bacillus are introduced into the lungs through the trachea, large areas of consolidation are formed (Fig. 449), which may involve whole lobes or whole lungs.

Microscopically, these consolidated areas are practically identical with those which are found in man in various forms of tuberculous bronchopneumonia. A later fibrous-tissue development may occur, and blood-vessels may be obliterated.

Fig. 448.

Fig. 449.

Fig. 448.—Experimental Tuberculous Inflammation (Miliary) in the Lung of a Rabbit. The rabbit's lung shows miliary foci of tuberculous inflammation twenty-two days after the injection through the trachea of a small quantity of broth culture of the tubercle bacillus.

Fig. 449.—Experimental Tuberculous Inflammation in the Lung of a Rabbit. Large areas of solidification in the lung twenty-eight days after the injection through the trachea of a considerable quantity of a pure culture of the tubercle bacillus. The lesions resemble those of acute phthisis in man.

In the presence of the tubercle bacillus alone the consolidated and caseous areas rarely soften and break down so as to form cavities. If, however, after the tuberculous lesion of the lung has been induced and allowed to continue for a number of days, a culture of Streptococcus pyogenes be introduced into the trachea of the rabbit, within twenty-four hours the caseous areas often begin to soften. The softening may begin at the center, or may surround a central portion of the necrotic mass. The softening is soon followed by absorption, and so cavities are formed of varying sizes and shapes (Fig. 450).

It will thus be seen that in the rabbit a concurrent infection with the tubercle

bacillus and the streptococcus has an important bearing upon the breaking down of lung tissue which leads to the formation of cavities. While it would not be wise to assume from these experiments on the rabbit that a similar condition is always present when cavities form in man, we have seen that in fact a similar concurrent infection in man in acute phthisis actually does often exist.

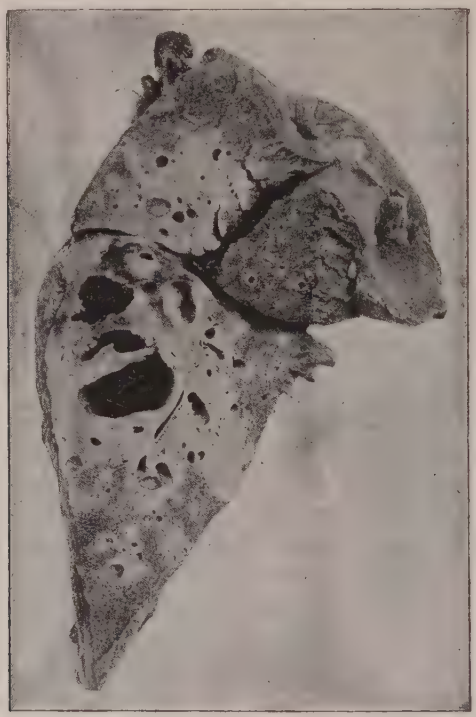


FIG. 450.—EXPERIMENTAL TUBERCULOUS INFLAMMATION IN THE LUNG OF A RABBIT, WITH THE FORMATION OF CAVITIES

The lung was injected with a considerable quantity of tubercle bacillus culture through the trachea, followed after twenty-eight days by the injection of the broth culture of the Streptococcus pyogenes. Animal killed seven days after the streptococcus injection. The specimen shows large areas of consolidation with cavities. The lesions resemble those of acute phthisis with cavities in man.

SYPHILITIC PNEUMONIA.

Persons suffering from inherited or acquired syphilis sometimes develop inflammations of the lungs which seem to be due to the syphilitic infection. The lungs may then be affected in several different ways.

There may be well-defined large or small gummata with or without interstitial and more or less exudative pneumonia. There may be a formation of new fibrous tissue in the walls of the bronchi and in the lung tissue about them, often with ulceration of the mucous membrane and distortion of these structures. There may be, particularly in the newborn, lobular or lobar hepatization, the affected region appearing reddish or gray or white. This is due to a growth of new cellular tissue in the

Pulmonary Tuberculosis—Exudative Type—with Large Cavities.

The entire lung is solid from new-formed tubercle tissue and exudate which are both largely in a condition of coagulation necrosis.

The thickened trunks of the larger pulmonary vessels are exposed in the depths of the ragged communicating cavities.

This lung was hardened in alcohol without injection of the blood-vessels.

walls of the air spaces and to an exudate largely of epithelial cells in the air spaces. Infarctions of the lung from obliterating endarteritis may be present. It is often difficult to determine in many cases of interstitial inflammation of the lungs whether the lesion be syphilitic or not.[1]

TUMORS.

Fibroma and **osteoma** are rare; **enchondroma** may occur as a primary tumor originating in the cartilages of the bronchi. **Teratoma** is an occasional finding.[2] **Sarcoma**[3] is not common and is usually secondary.[4]

FIG. 451.—SECONDARY CARCINOMA OF THE LUNG.
The primary tumor involved the gall-ducts, liver, and pancreas. The metastatic tumors in the lung were in part white, in part dark red from interstitial hemorrhage.

Mesothelioma (page 452), which is probably a carcinoma of peculiar morphology, is of infrequent occurrence on the surface of the lung, and,

[1] For a bibliography of pulmonary syphilis, consult *Flockemann*, Centralbl. f. Path., 1899, x, 449.
[2] *Katase*, Centralbl. f. allg. Path., 1912, xxiii, 146 (bibl.).
[3] For a study of sarcoma and carcinoma of the lungs, see *Packard*, Am. Jour. Med. Sc., 1917, cliv, 351. For primary sarcoma, see *Eckersdorff*, Centralbl. f. allg. Path., 1906, xvii, 355; *Pater* and *Rivet*, Arch. de méd. expér., 1906, xviii, 85; *Boschowsky*, Frankfurt. Ztschr. f. Path., 1912, ix, 239.
[4] *Holt* and *Ratterman*, Jour. Am. Med. Assn., 1916, lxvi, 171; *Jackson*, ibid., 833.

following the subpleural lymph-vessels may form a reticular raised white network (Fig. 452 and 453). **Adenoma** is rare.[1] **Carcinoma** is the most frequent of the primary tumors of the lung. In the past it has been considered one of the rare varieties of malignant neoplasms, but owing to the

FIG. 452.—MESOTHELIOMA OF THE PLEURA.
The inner surface of a segment of the costal pleura, containing three of the ribs, is shown in the cut.

improvement in diagnosis, due to the almost universal use of radiographs in searching for suspected tuberculosis, it has been found that a considerable proportion of persons under treatment for tuberculosis, without tubercle bacilli in the sputum, have an unsuspected carcinoma of the

FIG. 453.—MESOTHELIOMA OF THE PLEURA.
Showing the growth of the tumor along the superficial lymph-vessels.

lung. A considerable number of other persons suffering with vague symptoms, not always referable to the chest, have some type of diffuse carcinosis of the lungs. Such persons may die without any suspicion of a lung lesion.

In recent years autopsy statistics also have shown that there is a considerable increase in the number of cases of carcinoma of the lung in

[1] For a discussion of primary adenoma of the lung in mice, see *Tyzzer, E. E.*, Jour. Med. Research, 1909, N. S. xvi, 479.

Pulmonary Tuberculosis (Chronic), with Large Cavities.

The ragged communicating cavities involve a large part of the lung and are bronchiectatic in origin. The bronchial lymph-nodes are enlarged, tuberculous, and caseous. The pleura and interlobar septum are thickened by the formation of dense fibrous tissue.

Chronic Pulmonary Tuberculosis with a Fibrous-Walled Cavity at the Apex.

The fibrous wall of the cavity is dense and is continuous with the greatly thickened pleura and with the diffuse new-formed connective tissue throughout the upper lobe. The upper lobe is greatly reduced in size by the cicatricial contraction of the fibrous tissue. The lower lobe shows two areas of tuberculous consolidation; both are caseous in the central portions; the upper shows commencing tuberculous bronchiectasia. The upper part of the fibrous wall of the cavity, firmly adherent to the thoracic wall, has been cut away.

the general population. The earlier statistics showed that it formed about 1 per cent. of all types of carcinoma; now it forms 5 to 10 per cent.[1] Whether this is a sequela of the recent epidemics of influenza or whether it is due to inhalation of tar in particles of road dust, or to the inhalation of exhaust gases from motors, has been discussed, but is not settled. It is certain, however, that pulmonary tumors can be produced in animals by the irritation of the lungs with tar. In past years cancer was frequent in the lungs of the miners in the cobalt mines of Germany, the so called "Schneeberger" cancer. It was probably caused by the irritating dust from the ore.

The tumors occur more frequently in males than females and are most often found on the right side and in the upper lobe (Plate XIV-B2, Fig. 1 and 2).

The neoplasm usually arises from one of the bronchi, especially those of larger size, and is therefore chiefly of the alveolar type with cylindrical cells.

Squamous cell tumors,[2] gelatinous carcinomata, and medullary carcinomata composed of small cells are less frequent.[3] The squamous cell tumors are supposed to arise either by metaplasia of the bronchial epithelium or from the respiratory epithelium of the pulmonary alveoli. An occasional tumor has been found to have its origin in a tuberculous cavity.[4] If the growth fills a bronchus it may cause more or less complete stenosis, which usually leads to a gangrenous or suppurative involvement of the bronchial structures peripheral to the tumor, and may thus induce the formation of cavities of considerable size, but as a rule the tumors remain small and gradually involve more or less of the lung tissue. The growth may extend into the alveoli (Plate XIV-B2, Fig. 3) or it may invade the periarterial lymph spaces. Usually the bronchial lymph nodes are involved fairly early and the mediastinal pressure causes severe dyspnœa and cough which attracts attention to the lesion. Considerable areas, even whole lobes of the lung, may be filled with the growth (Plate XIV-B2, Fig. 4) and such invaded spaces are apt to soften and break down. Fragments of tumor are occasionally coughed up. Erosion of vessels may take place in these softening areas with moderate continuous or severe and rapidly fatal hemorrhage. The growth may involve the pulmonary pleura and even occupy a considerable portion of the pleural cavity. Some pleural exudate occurs in half of the cases and is often hemorrhagic. Tumor cells are sometimes demonstrable in the fluid. The involvement of the regional subcutaneous lymph nodes is not very frequent, though occasionally the supraclavicular or cervical group

[1] *Breckwoldt, R.*, Zeit. f. Krebsforsch, 1926, xxiii, 128 (bibl.) and *Biberfeld*, Med. Klinik, 1926, xxii, 1371.

[2] *Hermann, M.*, Ztschr. f. Krebsforsch., 1913, xiii, 446 (bibl.).

[3] *Adler*, Primary Malignant Growths of the Lungs and Bronchi, New York, 1912; *Henrici*, Jour Med. Research, 1912, N. S. xxi, 395 (bibl.); *Scott* and *Forman*, Med. Rec., 1916, xc, 452 (bibl.); *Lambert, R. A.*, Proc. New York Path. Soc., 1915, xv, 117.

[4] For bibliography, see *Wolff*, Die Lehre d. Krebskrankheit, Jena, 1911, Teil ii, 817; *Hermann*, Ztschr. f. Krebsforsch., 1913, xiii, 446; and *Oertel, H.*, Jour. Med. Research, 1911–12, N. S. xx, 503; for a discussion of the relation in general between carcinoma and tuberculosis, see *Layman*, Frankfurt. Ztschr. f. Path., 1914, xv, 360 (bibl.); *Bundschuh*, Zieglers Beitr., 1914, lvii, 64 (bibl. with special reference to the mamma).

may be invaded. The liver and bones are often invaded as is the brain.[1] While some of the brain metastases may be through the blood vessels, it is probable that most are the result of retrograde invasion of the perineural lymphatics of the cranial nerves.

Very rarely metastases occur in the skin or in a hypernephroma.[2]

Secondary tumors of the lung are extremely frequent following carcinomata of other organs. The usual path of invasion is through the lymphatics, and this is peculiarly frequent in carcinoma of the breast, often long after the operative removal of the primary tumor. The path for such metastasis is usually through the lymphatics which drain into the mediastinal or bronchial nodes and from there to the lungs or the pleura. The growth extends from the bronchial nodes through the lymph channels along the larger bronchi into the lung tissue, so that radiographs show a fork-like group of shadows outlining such bronchi (Plate XIV-B2, Fig. 2). Primary thymus tumors and esophagus tumors often take this path.

Certain other types of growths which are apt to travel by the blood stream, such as hypernephromata, chorioepitheliomata of the uterus or testicle, and especially sarcomata arising in the bone, are apt to form spherical masses in the lung tissue which appear in radiographs as the so called plaques (Fig. 451). The osteogenic sarcomata and the osteoplastic tumors of the prostate may give such definite shadows as to lead to the discovery of a heretofore unsuspected neoplasm in these situations. While many cases of carcinoma do not give rise to gross nodules in the lung, microscopic examination of this organ post-mortem will often show extensive involvement of the smaller vessels with tumor emboli. The cells of some may be actively growing, others are necrotic, being prevented from obtaining nourishment by a fibrinous envelope. The reason why such embolic particles do not more often form large tumors when even bone marrow and hence the vascular system is extensively involved, is apparently due to two causes. The first is that the high thrombokinase content of the tumor cell causes the deposition of fibrin on the cells which prevents their coming in contact with the wall of the veins and thus obtaining nutrition, and secondly, because of the respiratory movement of the lung which prevents the tumor cells from forming the prompt tissue connections which are necessary for their survival. Experimental demonstration of this fact is easy. If a grafted carcinoma in a rat or mouse is massaged and the animal is immediately killed, the lung capillaries will be found abundantly filled with tumor cells, but if a control animal is similarly treated and kept alive for a period of a month or two and then examined, only one or two growing carcinoma nodules will be found. All the other emboli have perished.

Pulmonary carcinoma of any type may be associated, especially in its later stages, with pneumonia of an exudative variety. The pnuemonia is usually patchy, involving small areas, but it may be extensive and of an irregular lobar type. Both the pneumococcus or the streptococcus may be found. Death may be very sudden from either pneumonia

[1] *Parker, H. L.*, Arch. of Neurol. & Psychiat., 1927, xvii, 198 (bibl.).

[2] *Rostoski, Saupe* u. *Schmorl*, "Schneeberger Lungenkrebs." Zeit. f. Krebsforsch., 1926, xxiii, 360.

FIG. 1.—LARGE SINGLE TUMOR FROM HILUS WITH A FEW SECONDARY NODULES IN BOTH LUNGS.

FIG. 2.—LARGE SINGLE TUMOR LEFT SIDE WITH EXUDATE IN PLEURA AND SMALL NODULE RIGHT SIDE AND FORK-LIKE THICKENING OF BRONCHI.

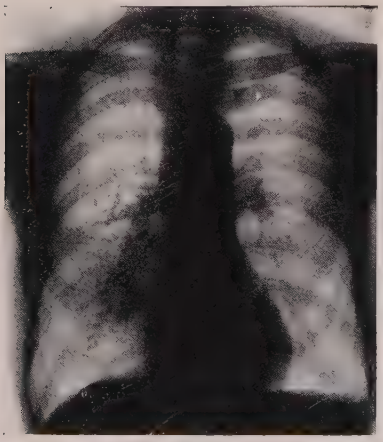


FIG. 3.—EARLY PRIMARY CARCINOMA OF LUNG DIFFUSELY INVOLVING THE PULMONARY TISSUE. THE PATIENT WAS WITHOUT SYMPTOMS.

FIG. 4.—LARGE SINGLE TUMOR FILLING LEFT CHEST AND PUSHING HEART TO RIGHT. SOME FLUID IN LEFT CHEST. LATE STAGE OF DISEASE.

Radiographs of Primary Carcinomata of the Lungs.

or cardiac failure due to the prolonged heart strain caused by the severe paroxysms of coughing constantly occurring in the later stages of the disease.

Dermoid cysts have been found in the lung.

THE MEDIASTINUM.

Inflammation.—Suppurative inflammation may occur in either the anterior or the posterior mediastinum. It may be caused by fractures, caries, or necrosis of the sternum and vertebræ, by perforation of the esophagus, by suppuration of the lymph-nodes, or by pleurisy, or may occur without discoverable cause.

Perhaps the most frequent cause in adults is the invasion of the posterior mediastinum of infectious material from the diseased vertebral bodies in Pott's disease. In adults a rare type is due to a descending infection from acute disease of the deeper tissue of the neck, such as retropharyngeal abscesses, Ludwig's angina, or similar phlegmonous processes. In children mediastinitis is usually due to retropharyngeal or peritonsillar streptococcal infections. In pneumonia some extension of the pleural inflammation to the mediastinum is the rule, though extensive suppurative lesions are rare. Metastatic abscesses, however, are not infrequent in adults following suppurative bronchopneumonias of influenza with or without a complicating empyema.

The pus may infiltrate the connective tissue, or may form abscesses which attain a large size. The inflammation may extend to the pleura or the pericardium, the abscesses may displace the heart, the lungs, or the sternum; or they may perforate through the skin, into a pleural cavity, the esophagus, the trachea, or a bronchus.[1]

A few cases of chronic inflammation of the tissues of the mediastinum have been reported—chronic mediastinitis.[2] The lesion is either due to syphilis, tuberculosis of a chronic type extending from the nodes or bony structures, or septic conditions which have not proved fatal in the initial acute phases. A diffuse infiltration and fibrosis may result without definite symptoms, or pressure on the superior cava may cause extreme cyanosis and oedema of the neck and face, sometimes extending to the chest and arms. Later huge dilatation of the veins of the upper extremity may occur. If the bronchi are compressed, cough, dyspnoea and paralysis of the left vocal cord may supervene.

Tumors.—The most common form of new growth in the mediastinum is *lymphosarcoma*, and the nodes of Hodgkin's disease. Leukemic tumors are rare.

These tumors are confined to the mediastinum, or they are associated with similar growths in other parts of the body. Persons between the ages of twenty and thirty years seem to be the most liable to the growth, but it is not uncommon in children. It begins in the lymph-nodes in the mediastinum, and at the root of the lung. It increases at first slowly, then more rapidly, and gradually infiltrates the adjoining tissues. In this way the walls of the trachea, bronchi, aorta, the pericardium, the pleura, and the lung, become infiltrated with compression of the surrounding organs.

Nodules of thyroid gland tissue may be found in the anterior mediastinum. Thyroid goiters may extend into the mediastinum and give rise to the same symptoms as chronic mediastinal inflammations. If carcinoma develops in such a retrosternal goiter the growth may cause absorption of the sternum and appear on the chest wall as a hard or pulsating tumor.

Complex tumors belonging among the fetal inclusions or teratomata are of occasional occurrence in the anterior mediastinum.[3] They may contain bone, cartilage, connective tissue, muscle, hairs, skin, and even chorionepithelioma, etc. Cysts, sometimes lined with ciliated epithelium, may form in such tumors.[4]

[1] For tuberculous lesions of the tracheobronchial lymph-nodes see reference, p. 683.

[2] *Whipham*, Lancet, 1899, i, 882, 947 (bibl.).

[3] See *Mandlebaum, F. S.*, Am. Jour. Med. Sc., 1900, cxx, 64.

[4] Consult *Hare*, Tumors of the Mediastinum, Philadelphia, 1889; also *Zahn*, Virchows, Arch., 1896, cxliii, 170 and 416; also *Lohrisch*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1900, vii, 912 (bibl.); also, for a study of dermoid cysts of the mediastinum, see *Morris*, Med. News, 1905, lxxxvii, 404, 438, 494, 538; *Lambert, S. W., and Knox, L. C.*, Intrathoracic teratomata, Trans. Am. Phys., 1920, xxxv, 17.

The Pleura.

HYDROTHORAX.

Non-inflammatory accumulations of clear serum in the pleural cavities are of frequent occurrence. They occur under conditions similar to those which lead to dropsy in other parts of the body—lesions of the heart, liver, and kidneys, and changes in the circulation and in the composition of the blood.

If the amount of serum be large it may compress the lower lobes of the lungs.

HYDROPNEUMOTHORAX—PYOPNEUMOTHORAX.

The presence of air in the pleural cavities is usually associated with a serous or purulent exudate. It may occur as the result of perforation of the lung, of rupture, of ulceration of tuberculous lesions at the pleural surfaces, of injuries to the chest wall, and of perforation of the diaphragm by suppurative or cancerous lesions of the esophagus, stomach, or intestine, as well as in a variety of other conditions. Gas may form in the pleural cavities in infection by the Bacillus aërogenes capsulatus.[1]

HEMORRHAGE.

Subpleural ecchymoses may occur in asphyxia or during infectious diseases or intoxications. More extensive extravasations of blood—hemothorax—may be the result of injuries to the wall of the thorax or the rupture of an aneurysm.

Hemorrhagic exudates (*hemothorax*) are usually associated with injuries, with malignant tumors of the lungs or pleura, with infarctions of the lungs, with tuberculous pleurisy, or with infectious diseases of a hemorrhagic type, and are occasionally seen in cases of cirrhosis of the liver.

INFLAMMATION. (Pleuritis, Pleurisy.)

Inflammation of the pleura may occur as an independent lesion, but it is commonly associated with pathological processes in the lungs, pericardium, abdomen, or chest wall. It may be exudative in character, usually associated with more or less proliferation of the mesothelial ("endothelial") and connective-tissue cells, or it may be productive with the formation of new connective tissue. These phases of inflammation may be associated. Through the production of new connective tissue, repair of the acute inflammatory lesion is commonly effected. In the exudative forms of pleurisy the exudate may consist of fibrin, or of serum and fibrin, or of serum, fibrin, and pus.

Simple Fibrinous Pleurisy (Dry Pleurisy; Pleuritis Sicca).—This may involve circumscribed areas of the costal, mediastinal, diaphragmatic, or pulmonary pleura, less frequently the entire pleura of one side of the chest. The affected portions of pleura are dull and lustreless and coated

[1] For a study of pneumothorax, see *Emerson*, Johns Hopkins Hosp. Rep., 1903, xi, 1.

with fibrin, opposing surfaces often being joined by bands of fibrin. There are swelling, degeneration, proliferation, and exfoliation of the mesothelium, with swelling and proliferation of the connective-tissue cells beneath. Exceptionally, there is involvement of the entire pleura of one side, with the production of such a large amount of fibrin as seriously to compress the lung.[1]

Serofibrinous Pleurisy (Pleurisy with Effusion).—This is the most common form of pleurisy. As a rule, it involves the greater part of the pleura of one side of the chest. Sometimes, however, the pleura of both sides of the chest is involved, and then the pericardium also is often inflamed.

While the inflammation is in progress the surface of the affected pleura is coated with fibrin, and bands of fibrin stretch between the parietal and pulmonary pleuræ. In the pleural cavity is serum in variable quantity. This serum is clear, or turbid from the presence of exfoliated mesothelium, leucocytes, and flocculi of fibrin or red blood-cells. The lung is compressed in different degrees and positions, according to the quantity of the serum and the character of the adhesions. The heart may also be displaced by the accumulated exudate.

The natural termination of such a pleurisy is the recovery of the patient, with thickenings of the pleura and adhesions. The irregular terminations are: The death of the patient, the protracted existence of the fibrin and serum, and the change of the character of the inflammation so that pus is produced.

If the patient recovers, the serum is absorbed, the fibrin disappears, and repair is effected, as in simple fibrinous pleurisy, by the formation of granulation tissue, which gradually becomes dense and cicatricial in character and may remain as local or general thickenings or firm adhesions of the opposed pleural surfaces. The lung may be distorted by contraction of the new-formed connective tissue. The exudates in the serofibrinous form of pleurisy do not usually infiltrate the pleura, but gather upon its surface and in the cavity.

The Excitants of Serofibrinous Pleurisy.—Cultivations from the exudate give in the larger number of cases negative results; but the pneumococcus, Streptococcus pyogenes, Staphylococcus aureus or albus, and the typhoid bacillus have been isolated. When the inflammation of the pleura is consecutive to acute lobar pneumonia, the pneumococcus may still not be found in the exudate. The presence of the streptococcus is frequently followed by the formation of pus. The organisms named above may be present alone or in various associations. Many cases with simple serofibrinous exudate prove on inoculation to be tuberculous.[2]

Suppurative Pleurisy (Empyema).—Suppurative pleurisy may occur either with or without the formation of a considerable serofibrinous

[1] For a study of the origin of fibrin and adhesions of the serous membranes, consult *Heinz, R.*, Virchows Arch., 1900, clx, 365; also *Gaylord, H. R.*, Jour. Exper. Med., 1898, iii, 1 (bibl.).

[2] For a study of the bacteria in exudative pleuritis, with the earlier bibliography, consult *Prudden*, New York Med. Jour., 1893, lvii, 696. For fuller data see *Netter*, Bouchard and Brissaud, Traité de Médecine, Paris, 1901, vii, 399.

exudate. The exudate may be purulent from the beginning, or a serofibrinous exudate may assume this character.

The pleural cavity in empyema is partly or completely filled with purulent fluid, and the lung is either compressed against the vertebral column or partly adherent to the chest wall. Sometimes, however, the purulent fluid is shut in by adhesions, either between parts of the lung and the thoracic wall, or between the lung and the diaphragm, or between the lung and the pericardium, or between the lobes of the lung.

The fluid in the pleural cavity is usually a thin, purulent serum, composed of serum, pus cells, mesothelial cells, and flocculi of fibrin; but sometimes this fluid is thick and viscid.

While in children the more or less active suppurative process in the pleural cavity may continue for a long time without deep involvement of the pleura, in adults granulation tissue may form upon the membrane, which thus becomes gradually thickened and may so remain for months with its inner vascular surface covered with pus and fibrin. In such cases, as well as in less chronic forms, the fibrin fibrils are often swollen and coalesce to form irregular homogeneous or finely granular masses. Resolution may occur in one region of the pleura while the exudate in another may become encapsulated by new-formed connective tissue.

In old cases the thickening of the pleura may be great and it may become calcified.[1] The perichondrium of the cartilages and the periosteum of the ribs may become inflamed, with necrosis of the cartilages and ribs or a production of new bone. Necrosis and gangrene of the involved pleura may occur and putrefactive process be set up in the exudate. The suppurative process may extend from the pleura involving adjacent parts, such as the fasciæ, the muscles, the skin, the diaphragm, or the lungs. Thus the pus may find an exit through the wall of the thorax, into the peritoneal cavity, or into the lungs.

In inflammation of the pleura the process may extend to the lymphatics in the interlobular septa, around the bronchi, and around the blood-vessels. This interlobular lymphangitis occurs more frequently in children than in adults. The lymphatics in the interlobular septa and those around the bronchi and blood-vessels are distended with pus cells, the septa are much thickened, and the lobules separated from each other.

Serofibrinous pleurisy and empyema may occur as complications of infectious diseases, such as scarlatina, typhoid fever, and various forms of septicemia, or by an extension of an inflammatory process from such adjacent parts as the pericardium, lungs, mediastinum, etc.[2] The various forms of pneumonia are frequently associated with local or general inflammation of the pleura.

The Excitants of Empyema.—Streptococcus pyogenes is the most frequent excitant of suppurative inflammation of the pleura. According to the statistics of Netter this organism has been found in a little over

[1] For a résumé of our knowledge of various calcifications in the lungs, and allied conditions often called "lung stones," consult *Polaillon*, Les Pierres de Poumon, Paris, 1891; or *Legry*, Arch. gén. de méd., 1892, i, 337 and 466.

[2] For a study of relation of esophageal diverticula to empyema, see *Starck*, Arch. f. Verdauungskr., 1901, vii, 1.

forty per cent. of the cases examined of all ages. The pneumococcus has been found in over twenty-five per cent. of cases examined. The streptococcus and the pneumococcus are associated in a small proportion of cases. Of less frequent occurrence are Staphylococcus pyogenes, Bacillus typhosus, Bacillus coli communis, the gonococcus, the pneumobacillus of Friedländer, and the influenza bacillus. In empyema with fetid exudate, various forms of bacteria may be present. While in the adult the streptococcus is most often found in the empyemic exudate, in young children the pneumococcus is, according to Netter,[1] most common.

Chronic Pleurisy with Adhesions.—This form of pleurisy may follow one of the varieties of pleurisy just described, it may be associated with emphysema and chronic phthisis, or it may occur by itself.

After death the pulmonary and costal pleura are found thickened and joined together by numerous adhesions. These changes may involve only a part or the whole of the pleura on one or both sides of the chest.

The thickened pleura is covered with mesothelium; the new connective tissue may be very dense and may contain few or many cells. Blood-vessels may be numerous and irregular in distribution or few in number. New lymph-vessels are formed with the growth of the new tissue.[2] These, as well as the old lymph-vessels, may be dilated, forming small cysts.

Tuberculous Pleurisy.—Acute general tuberculosis of the pleura is usually secondary to tuberculous inflammation elsewhere in the body, either in the lungs, which is most common, or the bronchial lymph-nodes, peritoneum, bones, etc., or it may be a part of a general miliary tuberculosis. There may be localized or widely disseminated miliary tubercles upon or beneath the pleural surfaces, either in direct association with lesions beneath the pulmonary pleura or apart from these or upon the costal pleura. The tuberculous foci may be larger and more diffuse. The minute characters of the inflammation are not essentially different from those found in tuberculosis in connective tissue elsewhere, but the mesothelial cells covering the pleura may share largely in the early phases of the new growth.

If the process is prolonged, much dense fibrous tissue may be formed in which are miliary tubercles in various stages of coagulation necrosis, or larger patches of necrotic tissue surrounded by miliary tubercles or diffuse tuberculous tissue.

With acute types of tuberculous inflammation of the pleura more or less exudate may form. This may be serofibrinous, often with very little fibrin, or, as is frequently the case, it may be tinged or deeply colored with blood. The exudate may be purulent. The tubercle bacillus may be associated with other bacteria, most often with the Staphylococcus pyogenes in the purulent exudate.

Many cases of pleuritis with a serofibrinous exudate giving no growth

[1] *Netter*, Bouchard and Brissaud, Traité de Médecine, Paris, 1901, vii, 445. For a study of the ways of infection of the pleura, see *Grober*, Deutsch Arch. f. klin. Med., 1900, lxviii, 296 (bibl.).

[2] For a study of the formation of new lymph-vessels in pleurisy, see *Guyot, G.*, Zieglers Beitr., 1905, xxxviii, 207.

of bacteria on the ordinary culture media are found to be tuberculous, by the inoculation of guinea-pigs with the fluid.

Miliary tubercles of the pleura, chronic in form, mostly composed of fibrous tissue, with cheesy degeneration or calcification, are very common, and are frequently associated with tuberculous bronchial lymph-nodes without tuberculosis in other parts of the body. These tubercles are usually widely scattered over the pleura and are almost always associated with anthracotic pigmentation.

The dense fibrous tubercle or the cheesy or calcified portion may be seen as a lighter spot in the pigmented area (Fig. 416). Such tubercles are sometimes accompanied by minute cystic dilatations of the lymph-vessels on which they are formed.

These pleural tubercles develop along the subpleural lymphatic vessels, or in the areas of lymphoid tissue or in the minute subpleural lymph-nodes.

The presence of these healed tubercles, which rarely harbor stainable tubercle bacilli, together with the simultaneous involvement and pigmentation of the bronchial lymph-nodes, affords strong evidence of the frequency of the direct infection of the lungs through the respiratory passages. They are formed along the lines of lymph drainage of the lungs which ultimately enter the bronchial nodes. Since in this drainage inhaled pigment particles and tubercle bacilli are deposited together, the frequent association of pigmentation and tuberculosis is comprehensible.

Hodenpyl showed the great frequency of those chronic pleural pigmented tubercles, and Ribbert[1] believed that the tuberculous process precedes the local pigmentation and furnishes suitable conditions for it.

TUMORS.

Benign tumors of the pleura are rare, though **fibroma** and **enchondroma** have been described;[2] **fibromata** and **lipomata** developing in the

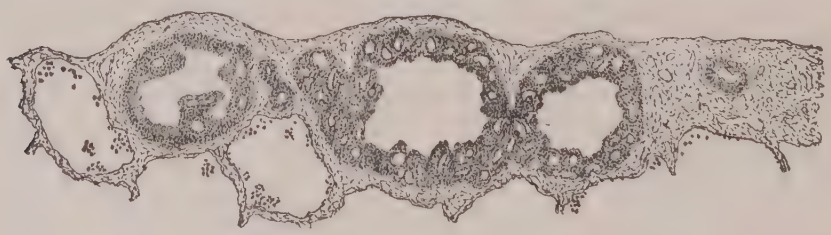


Fig. 454.—Mesothelioma (Endothelioma) of the Lung.

The growth is in the subpleural lymph-vessels, which seen from the pleural surface in the fresh lung formed a white raised network over a considerable portion of one lung. The lymph-vessels in the cut are seen in transverse section.

subpleural tissues may encroach upon the pleural cavity. Small, white, slightly projecting, often pigmented elevations of the pleura, either single

[1] *Ribbert*, Deutsch. Med. Wchnschr., 1906, xxxii, 1615.

[2] For a discussion of tumors of the pleura in general, see *Pallasse* and *Roubier*, Ann. de méd., 1916, iii, 243 (bibl.).

or multiple, are common. These were formerly regarded as miliary fibromata, but Hodenpyl[1] and others have shown that while some may be fibromata, lymphangiomata, or air cysts, the majority are fibrous masses replacing or inclosing miliary tubercles.

A malignant growth of the pleura which is variously called **mesothelioma, sarcoma,** or **endothelioma**[2] (page 451), is an occasional finding; it occurs in the form of flat or projecting irregular nodular masses of various size (Fig. 454), frequently most distinct and extensive upon the costal pleura (Fig. 451 and 452). This, as well as other neoplasms of the pleura, may be associated with exudative pleuritis.

Carcinoma, primary in the thyroid, mamma, esophagus, or stomach, may invade the pleura.

Echinococcus and other **cysts** of the pleura have been recorded.[3]

[1] *Hodenpyl*, Med. Record, 1899, lv, 903.

[2] *Bernard*, Virchows Arch., 1913, ccxi, 156; *Mehrdorf*, ibid., 1908, cxciii, 92; *Glockner*, Ztschr. f. Heilk., 1897, xxviii, 209.

For a discussion of both pathological and clinical aspects of these tumors, see *Fraenkel*, Deutsch. med. Wchnschr., 1911, xxxvii, 531; and *Pick*, ibid., 570.

For a discussion mainly from the clinical side, see *Keilty*, Am. Jour. Med. Sc., 1917, cliii, 888. See also *Robertson* who believes all pleural malignant growths to be secondary to carcinoma of the lung. Jour. Cancer Research, 1924, viii, 317.

[3] For a description of ciliated cysts of the pleura, see *Zahn*, Virchows Arch., 1896, cxliii, 170.

CHAPTER VII.

THE DIGESTIVE SYSTEM.

The Mouth.

Malformations.

Malformations of the lips and cheeks are usually associated with defective formation of the bones of the mouth. The entire process is generally due to an arrest of development, or a failure of the nasal and maxillary processes or of the branchial arches to fuse normally (see Fig. 185, 186 and 455).

1. The lower jaw is absent; the upper jaw and hard palate are small and imperfectly formed; the temporal bones nearly touch in the median line. The lower part of the face is, therefore, wanting; the mouth is absent, or small and closed posteriorly; the tongue is absent. Such a malformation is rare; the fetus is not viable.

2. The face remains in its early fetal condition of a large cleft; the mouth and nose form one cavity; the orbits may be united in the same cavity. The fetus is not viable.

3. There is a cleft in the upper lip, upper jaw, and hard palate. The cleft corresponds to the point of junction of the processes of the superior maxilla with the intermaxillary bone. There may be one cleft or two, one on either side of the intermaxillary bone. The cleft involves the lip alone,—harelip (Fig. 186 and 187)—or the lip and superior maxilla, or the lip, maxilla, and palate. There may be a single, or a double cleft in the palate, and the cleft may involve either the hard or soft palate, or both. If there are two clefts of the lip and maxilla the portion of lip and bone between them may be small, or entirely absent so as to leave a large open space. The soft palate may be entirely absent. This is a common malformation and does not endanger life.

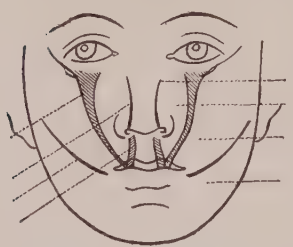


Fig. 455.—Diagram of Lines of Embryonic Union in Face.
Showing the position of clefts of the upper lip. (Merkel.)

4. Rarely there is a cleft involving the middle of the lower lip, and sometimes extending into the inferior maxilla.

5. Either the inferior, or the superior, or both maxillary bones may be abnormally small.

6. The edges of the lips may be partly or completely joined together. The opening of the mouth may be only a round hole.

7. The lips may be absent or imperfectly developed.

8. The corners of the mouth may be prolonged by clefts in the cheeks nearly to the ears.

INFLAMMATION. (Stomatitis.)

Catarrhal stomatitis is most frequent in children and occurs with a great variety of local and general disturbances.

During life the congestion and swelling of the mucous membrane may be well marked and there are often white patches, produced by the death of the superficial epithelial cells. There may be an increased production of mucus, or, instead of this, the entire mucous membrane may be un-

naturally dry. In addition to hyperemia and local edema there may be proliferation, exfoliation, and degeneration of the epithelium.

Extravasated leucocytes may infiltrate to a moderate degree the stroma of the mucous membrane and appear upon its surface. Small, clear vesicles may form beneath the epithelium from the collection of serous exudate.

Croupous stomatitis is incited by local irritants, by local infection, or by the extension of the same form of inflammation from the pharynx; it frequently occurs with diphtheria and other infectious diseases.

Portions of the mucous membrane are swollen and congested, and covered with a false membrane. This false membrane is composed of a thickened layer of epithelium in the condition of coagulation necrosis, and of fibrin and pus in variable relative quantity. The stroma of the mucous membrane may be infiltrated with pus and fibrin, and portions of it may become necrotic.

Aphthous Stomatitis.—In this condition small whitish projecting patches surrounded by a zone of hyperemia may form upon the mucous membrane. These consist of a more or less fibrinous exudate beneath the epithelium which may exfoliate, leaving small ulcers.

Ulcerative Stomatitis.—This form of stomatitis is apt to occur in ill-nourished children or in young adults, in scurvy, or in mercurial poisoning. It usually begins at the margin of the gums of the lower jaw and extends to the cheeks and tongue. The affected parts are swollen and coated with a grayish, soft pellicle composed of bacteria and necrotic tissue. The gums may be destroyed around the teeth, and these may fall out. The surrounding soft parts are swollen, and there may be necrosis of the jaws. Chronic phosphorus poisoning, also, induces a severe inflammation with necrosis of the maxillary bones.

In **noma** or **gangrenous stomatitis** similar changes may be associated with extensive gangrenous destruction of the cheeks. This most often occurs in young children in connection with measles, scarlatina, or typhoid fever. It has been asserted that a special microorganism is the excitant of this disease, but this has not yet been proved.

Thrush (Soor; Parasitic Stomatitis).—In ill-nourished children or in adults suffering from chronic disease a fungus related to the yeasts—*oïdium albicans*—may grow among the epithelial cells of the mouth, forming white membranous patches. These may involve large areas of the mouth and pharynx and extend to the esophagus or upper respiratory passages.

Phlegmonous Stomatitis.—Exudative inflammation of the mouth may result from infected wounds, in connection with erysipelas or suppurative or other infectious process near the mouth. Various pyogenic bacteria may be its excitants.

Chronic Stomatitis.—This may follow acute catarrhal or other inflammatory processes, or most frequently syphilis, and may be due to persistent irritation—for example, from the use of tobacco. Owing to hyperplasia of the epithelium and submucous tissue, white patches of varying extent may form on the tongue or elsewhere—*leucoplakia buccalis.*

These through excessive increase in the epithelium may project in wart-like form from the surface—*ichthyosis*. When the thickening is accompanied by local inflammatory thinning it produces the condition known as *geographic tongue*. The inflammatory lesion is apt to be more extensive than in simple leucoplakia.

Fig. 456.—Fibrous Epulis from Gum.

This type contains only fibrous tissue with large vessels, in contradistinction to the more usual giant-cell type.

Tuberculous stomatitis commences with the formation of miliary tubercles or of larger tuberculous masses in the stroma of the mucous membrane. These masses soon degenerate, soften, and form ragged ulcers.

Syphilitic Stomatitis.—As a result of syphilis there may be produced either the so-called mucous patches or gummata. In the mucous patches the epithelial layer is at first thickened and the papillæ of the stroma are swollen and infiltrated with cells (see Fig. 167, p. 311 and Fig. 168, p. 312). This may be followed by desquamation of the epithelium and ulceration.

TUMORS.[1]

Fibroma, lipoma, and **enchondroma** have been seen in a few cases in the lips. When in the mouth they usually grow from the bones. **Epulis,** which may be congenital,[2] is a tumor of the jaw, either fibrous (Fig. 456), sarcomatous, or epitheliomatous. The term is applied in a clinical sense to any tumor of the jaw, but the most frequent form is the giant-cell sarcoma (see page 443).

Fig. 457.—Tumor of Hard Palate.

These tumors are related both in morphology and in nature to those of the salivary glands.

Papillomata occur most frequently at the edges of the lips, but are found also on the gums, the floor of the mouth, and the cheeks. They are composed of hypertrophied papillæ covered with thickened epidermis, and often ulcerate. **Angiomata** may be formed in the mucous membrane covering the mouth, lips, or soft palate. These tumors are rounded, usually small, though sometimes as large as a hen's egg, and may be situated in the mucous membrane or project from it as a polyp.

Mixed tumors, like those found in the parotid gland (page 453 and 809), sometimes arise in the palatine region (Fig. 457).[3]

[1] For a general discussion of tumors and other diseases of the mouth, see *v. Mikulicz-Radetsky* and *Kümmel*, Die Krankheiten des Mundes, Jena, 1909; *Blessing*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1914, xvii[1], 858; and *Means* and *Forman*, Jour. Am. Med. Assn., 1917, lxviii, 180.

[2] *Füth*, Beitr. z. Gebürtsh. u. Gynäk., 1902, vi, 82.

[3] *Sturgis*, Surg., Gynec., and Obst., 1914, xviii, 456 (bibl.).

Carcinoma is of frequent occurrence and is usually of the epitheliomatous form. It may originate from any part of the mucous membrane of the mouth, and often develops on the edge of the lower lip as a result of persistent irritation by a clay-pipe or in the mucous membrane of the cheek from the irritation of a rough or carious tooth. Carcinomata may originate in an ulcerating papilloma, as flat superficial growths from the deeper layers of the epithelium, or as deep nodules starting in the mucous glands.

Dermoid tumors have been described[1] in the floor of the mouth.

Cysts.—Dermoid cysts and cysts of the embryonal branchial clefts may involve the mouth, the latter sometimes giving rise to carcinoma.[2] Simple cysts may form in the jaws from aberrations in the development of the teeth. Complex congenital tumors of the mouth are of rare occurrence, apparently arising in some congenital anomaly.[3] For a description of adamantinoma, see page 458.

FIG. 458.—THYROGLOSSAL DUCT FROM BASE OF TONGUE.
Showing ciliated epithelium and remnants of thyroid tissue about the periphery.

The Tongue.

Malformations.

Absence of the tongue may be associated with the extreme defects of development of the face already mentioned.

The anterior portion of the tongue may be absent while its base remains. The lower jaw is then small. The tongue may be cleft or lobulated.

It may be partly or completely adherent to the floor of the mouth. The frenulum may be abnormally short, or may extend to the tip of the tongue. In rare cases the

[1] *Hassel*, Beitr. z. klin. Chir. (Bruns), 1913, lxxxiii, 332 (bibl.); *Gilman*, Surg., Gynec., and Obst., 1916, xxii, 672.

[2] *Powers*, Ann. Surg., 1898, xxvii, 187 (bibl.).

[3] For a study of complex tumors of the mouth, see *Schorr*, Zieglers Beitr., 1906, xxxix, 82.

sides of the tongue are adherent, or its upper surface may be adherent to the roof of the mouth.

Ciliated or colloid-containing cysts at the base of the tongue are derived from remnants of the thyroglossal duct (Fig. 458).

HYPERTROPHY AND INFLAMMATION.

Macroglossia, or *hypertrophy* of the tongue, is almost always a congenital lesion, and is especially common in cretins. The tongue may be so large that it protrudes through the lips. The lips may also be similarly enlarged. There is hyperplasia of the fibrous and other tissues of the tongue, and in addition to this there may be a dilatation of the lymphatic vessels. Macroglossia is seen, also, in acromegaly.

Inflammations of the tongue—*glossitis*—may be associated with similar changes in the mouth, or may occur by themselves. In catarrhal inflammation the accumulation of epithelium may give rise to the "furred tongue." Most of the inflammatory processes above indicated as occurring in the mouth may affect the tongue also, especially leukoplakia, which is important as a possible precancerous condition. Tuberculous lesions in the form of shallow ulcers are not infrequent in those suffering from pulmonary tuberculosis. Primary and tertiary syphilitic lesions, also, are occasionally seen, and especially an atrophy of the papillæ and glands at the base of the tongue which is thought to be diagnostic of syphilis. In addition to the smooth atrophy a sclerotic process may ensue which renders the organ very hard and stiff.

TUMORS.

Hyperkeratosis linguæ (*black hairy tongue*) is an occasional finding,[1] and papillomata are not rare.

Cysts.—The most common forms of cysts are the sacs beneath or partly in the substance of the tongue (*ranula*). They are formed by dilatation of the ducts of the mucous glands or of the submaxillary and sublingual glands. **Amyloid** or **colloid tumors** of the tongue have been reported,[2] as well as thyroid and parathyroid tumors.[3] If the thyroid gland is atrophic, these tumors may act vicariously and prevent myxedema.[4]

Lipoma and **fibroma** are rare. They form nodules in the substance of the tongue or project in a polypoid form. Composite tumors, composed largely of fat, are found on the tongue as a congenital condition.

Angioma.— Cavernous vascular tumors are found in the substance of the tongue or projecting from its surface.

Sarcoma[5] is not common in this situation. **Carcinoma,**[6] usually of the epitheliomatous type, is a much more frequent growth, affecting

[1] *Arrowsmith*, Laryngoscope, 1909, xix, 545 (bibl.).

[2] *Heller*, Wien. klin. Wchnschr., 1908, xxi, 1383 (bibl.). See *Schmidt*, Virchows Arch., 1896, cxliii, 369, for bibl. of amyloid tumors in general. For additional bibl. of amyloid tumors, see page 676.

[3] *Wood*, Proc. New York Path. Soc., 1916, xvi, 84 (bibl.).

[4] *Ungermann, E.*, Virchows Arch., 1907, clxxxvii, 58 (bibl.).

[5] *Baastrup*, Arch. f. Laryngol. u. Rhinol., 1912, xxvi, 379 (bibl.).

[6] For the differential diagnosis of various ulcers of the tongue, see *Howell-Evans*, Brit. Med. Jour., 1912, i, 1283.

particularly the male sex, perhaps because of the irritation to which the tongue is subjected during the use of alcohol and tobacco. Syphilis is said to be an important predisposing factor.

MICROORGANISMS OF THE MOUTH.

Microorganisms of various forms—bacteria, moulds, and yeasts—are always present in the mouth, often in enormous numbers. They are for the most part not of significance save for the putrefactive processes which they initiate and maintain in mouths not properly cleansed. On the other hand, Staphylococcus and Streptococcus pyogenes and the pneumococcus are of frequent occurrence in the mouths especially of those who live in towns and crowded dwellings, and, while usually harmless, they may under favorable conditions become excitants of serious disease.

The tubercle bacillus may be present in the mouth as well as in the nose of those who care for uncleanly consumptives.

The fungus of thrush (soor), and leptothrix, which under usual conditions are not harmful, may incite serious local disease.

The so-called Mycosis pharyngis is apparently due to the growth in susceptible persons of a form of leptothrix not yet thoroughly studied, on account of the technical difficulties in the way of its artificial cultivation.[1]

Two cases of granulomata of the tongue, thought to be due to blastomycetes, have been described.[2] Actinomycosis, also, has been reported.

The Pharynx and Tonsils.

Malformations.

Branchial Fistulæ and Cysts.—When, as not infrequently occurs, the embryonal gill clefts do not close properly, *fistulæ* may remain.[3] These may in rare cases be complete, so that an opening exists from the pharynx, larynx, or trachea to the side of the neck (see Fig. 185, p. 367). More frequently, however, these fistulæ are incomplete and shallow, and open either inward into one of the above-named organs or outward on to the neck. Small portions of the gill clefts may persist without external openings, and from these subcutaneous *cysts* of the neck are often developed. Or a portion of the cleft may be cut off, forming a cyst, while the fistula persists with its external opening. The possibility that some, if not all, of these cysts and fistulæ may be derived from the embryonic ducts of the lateral lobes of the thyroid and the thymus bodies, has been suggested.[4]

The walls of these fistulæ and cysts may be covered with mucous membrane having cylindrical or flattened or ciliated surface cells. Or, when formed from the outer clefts, they may be lined with skin.

Not infrequently the walls of these cysts and fistulæ are embedded in lymphatic tissue, which may be diffuse or gathered in nodular form (see Fig. 459 and 460).[5]

Diverticula of the pharynx have been observed.

[1] For methods of cultivating spirochetes (Treponema) found in the mouth, see *Noguchi*, Jour. Exper. Med., 1912, xv, 81; and 1912, xvi, 194.

[2] *New, G. B.*, Jour. Am. Med. Assn., 1917, lxviii, 186.

[3] For details of the formation of fissures in the cervical region from incomplete closure of the branchial clefts, see *Thoma*, Text-book of General Pathology, Eng. trans , 1896, p. 201; and *Grosser*, Keibel and Mall, Human Embryology, Philadelphia, 1912, ii., 446.

[4] *Wenglowski*, Arch. f. klin. Chir. (Langenbeck), 1913, c, 789 (bibl.).

[5] For bibliography of branchial cysts and fistulæ, see *Coplin, W. L.*, Proc. Path. Soc., Philadelphia, 1901, N. S. iv, 109.

INFLAMMATION. (Pharyngitis, Angina, Tonsillitis.)

Catarrhal pharyngitis is usually associated with the same form of inflammation in the mouth and has similar characters.

FIG. 459.—SECTION OF THE WALL OF A BRANCHIAL CYST OF THE NECK.
Formed from the imperfect closure of an embryonal gill cleft. The cyst is lined with ciliated epithelium, and the wall is largely formed of diffuse lymphoid tissue.

FIG. 460.—SECTION OF THE WALL OF A BRANCHIAL CYST OF THE NECK.
This cyst, like that shown in Fig. 447, has much lymphoid tissue in the wall, but is nodular in character, while the epithelial lining is squamous in type.

In catarrhal inflammation involving the tonsils and those portions of the pharynx richly supplied with the so-called submucous adenoid—lymphoid—tissue, leucocytes may in considerable numbers pass through

the thin epithelial layer and mingle with the exudate upon the exposed surface.

In chronic inflammation of the pharynx there may be a large and permanent hyperplasia of the lymphoid tissue, with more or less dense fibrous tissue, leading to diffuse or circumscribed nodular or pedunculated masses of vascular new tissue in the vault or elsewhere in the pharynx, called "adenoids."[1]

Phlegmonous pharyngitis may occur with inflammations of the mucous membrane, with caries of the cervical vertebræ, with inflammation of the cervical and parotid glands, and with periostitis of the cranial bones, or it may occur independently. It may result in swelling and edema, in induration, or in suppuration. It is most important when it affects the posterior wall of the pharynx and forms retropharyngeal abscesses. Such abscesses may cause death by suffocation.

Diphtheritic pharyngitis is the form of pseudomembranous or croupous inflammation of which the Bacillus diphtheriæ is the excitant. The general characters of the diphtheritic infection have been considered in an earlier part of this book. The local process, often affecting the fauces, pharynx, and tonsils, may involve the mouth as well as the larynx and trachea (for details of the local lesion see page 319).

Tonsillitis.—The tonsils may share in the inflammatory processes of the pharynx or be independently affected. The structural characters of the tonsils render them liable to infection and involve certain peculiarities in the lesions.[2]

In Follicular Tonsillitis the swollen organ shows upon section an increase in the number of the lymphoid cells of the nodules and a hyperplasia of the endothelium of the reticulum. These new-formed and often exfoliated endothelial cells are similar to those found in the lymph-nodes in general in the presence of bacterial or other toxic substances. There may be an increase in the cells of the stroma of the tonsil. The epithelial cells of the surface and the crypts may increase in number and exfoliate. Epithelial cells and leucocytes and other forms of exudate may gather in the crypts or over the surface of the tonsil, forming white plugs or a whitish pellicle.[3] Thrombi are often found in the vessels.

In Exudative Tonsillitis (*suppurative* or *phlegmonous tonsillitis, quinsy*) there are, in addition to hyperplasia and catarrhal inflammation, edematous swelling and suppuration leading to a peritonsillar abscess.

Acute inflammation of the pharynx and tonsils is usually infectious in character, and may be due to various forms of pyogenic and other organisms. Thus in tonsillitis and other forms of acute angina, the most common microorganisms concerned are Streptococcus[4] hemolyticus and

[1] See page 672. For a study of the uvula in various abnormal conditions, see *Hoen, A.G.*, Jour. Exper. Med., 1898, iii, 549.

[2] Consult *Dobrowolski, Z.*, Zieglers Beitr., 1894, xvi, 43.

[3] See *Hodenpyl, E.*, Am. Jour. Med. Sc., 1891, ci, 257; also *Packard*, Philadelphia Med. Jour., 1900, v, 914, 957. For a study of the lymph drainage of the faucial tonsils, see *Wood, G. B.*, Am. Jour. Med. Sc., 1905, cxxx, 216. For a study of absorption in the tonsils, see *Wright*, New York Med. Jour., 1906, lxxxiii, 17.

[4] See, for study of milk-borne epidemic of tonsillitis due to streptococci, *Smith* and *Brown*, Jour. Med. Research, 1914–15, N. S. xxvi, 455.

viridans, the Staphylococcus, the pneumococcus, and many others.[1]

In Chronic Tonsillitis (the so-called hypertrophy of the tonsils) there is hyperplasia of the lymph-nodules with increase in the fibrous stroma. The mouths of the crypts may be occluded and distended with exfoliated cells and cell detritus; these deposits may become calcified.[2] Hemolytic streptococci are often present but are of no pathological significance.

Tuberculous Pharyngitis.—Tuberculous inflammation of the pharynx may be primary or secondary to tuberculous lesions elsewhere; ulcers

Fig. 461.—Tuberculosis of Tonsil.

may form and the tonsils may be involved. This infection may be primary and may be due to either the human or the bovine type (Fig. 461).[3]

The hyperplasiæ of the pharyngeal mucosa in children, commonly called "adenoids," have been found in a considerable number of cases to be tuberculous. The fact should be borne in mind that from tuberculous adenoids and tonsils tubercle bacilli may pass through the lymph-channels to the bronchial and cervical lymph-nodes, and that the pharynx may thus be a more important portal of entry in tuberculosis than has hitherto

[1] For a study of actinomyces-like structures in the tonsillar crypts, see *Gappisch*, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 130; also *Wright, J.*, Am. Jour. Med. Sc., 1904, cxxviii, 74. For study of bacteriology and pathology of tonsils with reference to articular rheumatism and cardiac disease, see *Davis, O.*, Jour. Infect. Dis., 1912, x, 148.

[2] For résumé of tonsillar calculi with bibliography, see *Robertson*, Brit. Med. Jour., 1899, i, 14.

[3] For a study of primary tonsillar tuberculosis, see *Mitchell, A. P.*, Jour. Path. and Bacteriol., 1917, xxi, 248 (bibl.); and *Cobbett, C.*, Causes of Tuberculosis, London, 1917, p. 590.

been recognized.[1] These nodes, when tuberculous, have frequently been shown to contain bacilli of the bovine type, an observation pointing to infection by means of food.

TUMORS OF THE PHARYNX.[2]

Fibromata grow from the periosteum of the bones at the base of the skull and project into the cavity of the pharynx and posterior nares in

FIG. 462.—"ADENOID" POLYP OF PHARYNX.

the form of large polypoid tumors. Other *retropharyngeal* tumors,[3] both benign and malignant and of various types, occur (*myxofibroma, fibrolipoma, fibrochondroma, sarcoma*, etc.).

Lipomata[4] and **amyloid tumors**[5] are occasionally discovered in the pharynx and larynx.

[1] For a study of the tonsils as portals of entry of tubercle bacilli, see *v. Scheibner*, Zieglers Beitr., 1899, xxvi, 511; also *Friedmann, F.*, ibid., 1900, xxviii, 66. Also bibliography in *Wood, G. B.*, Univ. Pennsylvania Med. Bull., 1903, xvi, 368. For relation of cervical and bronchial lymph-nodes to tuberculous infection, see *Beitzke, H.*, Virchows Arch., 1906, clxxxiv, 1.

For general bibliography on the tonsils, see *Ullman*, Med. News, 1901, lxxviii, 137.

[2] For general discussion of tumors of the pharynx, see *Schellong*, Geschwülste des Pharynx, Diss. med., Göttingen, 1897; of malignant tumors of the nasal pharynx, see *Opikofer*, Arch. f. Laryngol. u. Rhinol., 1913, xxvii, 526.

[3] *Brunner*, Beitr. z. klin. Chir. (Bruns), 1903, xxxvi, 689 (bibl.); *Hellendall*, ibid., 1903, xxxix, 666 (bibl.).

[4] *Goebel*, Deutsch. Ztschr. f. Chir., 1904, lxxv, 196 (bibl.).

[5] *Secket*, Arch. f. Laryngol. u. Rhinol., 1912, xxvi, 1 (bibl.).

Soft polypoid masses consisting largely of loose succulent connective tissue and lymphoid tissue and often called **adenoid polyps** (Fig. 462), are of frequent occurrence. They are usually to be regarded rather as hyperplasiæ than as true tumors.

Hairy polyps (*teratomata*) of the pharynx have been described.[1]

Sarcoma, carcinoma,[2] and various tumors of mixed type are of frequent occurrence in the pharynx.

Cavernous angiomata[3] may develop in the posterior pharyngeal wall.

TUMORS OF THE TONSIL.

Aberrant islets of cartilage, bone, and marrow are sometimes discovered in the tonsil (Fig. 463);[4] these, however, are not in any sense true tumors.

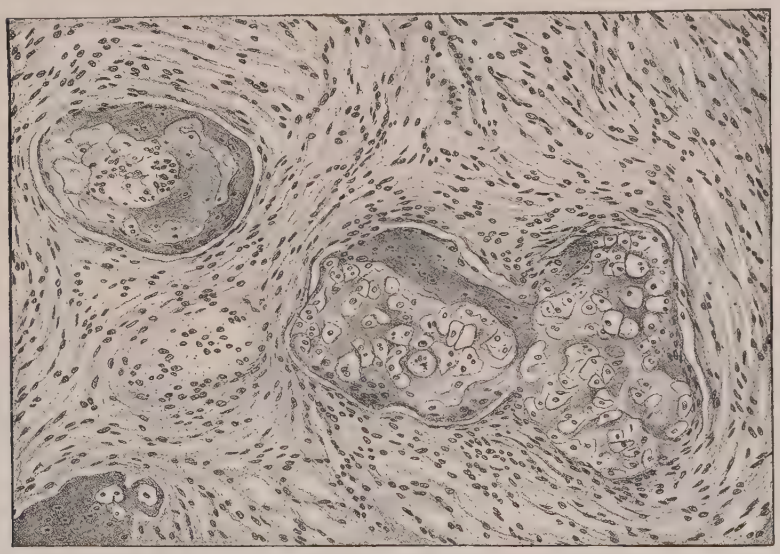


FIG. 463.—CARTILAGE, BONE, AND BONE-MARROW IN PERITONSILLAR TISSUE.

Lipoma[5] has been described. Malignant tumors[6] are comparatively rare, though both **carcinoma** and **sarcoma**[7] have been found. **Teratomata**[8] also occur. Metastatic carcinoma is distinctly uncommon.[9]

[1] *Reuter*, Arch. f. Laryngol. u. Rhinol., 1905, xvii, 233 (bibl.).
[2] For a study of carcinoma originating in the branchial clefts, see *Powers*, Ann. Surg., 1898, xxvii, 187.
[3] *Blau*, Arch. f. Laryngol. u. Rhinol., 1912, xxvi, 270 (bibl.).
[4] *Cary, E. G.*, Proc. New York Path. Soc., 1916, xvi, 173 (bibl.).
[5] *Sommer*, Arch. f. Laryngol. u. Rhinol., 1906–07, xix, 523 (bibl.).
[6] *Mathews*, Laryngoscope, 1912, xxii, 737 (bibl.); *Honsell*, Beitr. z. klin. Chir. (Bruns), 1895, xiv, 736.
[7] *Berry*, Boston Med. and Surg. Jour., 1912, clxvi, 376.
[8] *Jewett*, Laryngoscope, 1909, xix, 366; *Quarella*, Policlinico, 1917, xxiv, 60 (abstr. in Jour. Am. Med. Assn., 1917, lxviii, 1441).
[9] *Stoll*, Arch. f. Laryngol. u. Rhinol., 1913–14, xxviii, 267 (bibl.).

The Esophagus.

Malformations.

Malformations of the esophagus are rare. The esophagus may be entirely absent or its lower portion may be present and joined to the pharynx by a solid cord; or the pharynx, or the lower part of the esophagus, may be continuous with the trachea; or the entire esophagus may be represented by a solid cord. Dilatations of the esophagus and division of the middle portion of the esophagus into two branches have been observed.[1] The mucosa may be folded across the lumen partially occluding it.

PERFORATION AND RUPTURE.

Foreign bodies in the esophagus may perforate its wall. Perforation of the esophagus from without may be produced by inflamed bronchial glands, by the extension of cavities and gangrene of the lungs, by abscesses in the mediastinum, by abscesses accompanying caries of the vertebræ, and by aneurysms of the aorta. Rupture of the wall of the esophagus by violent coughing and vomiting has been described, but it seems improbable that this should occur without some previous local lesion.[2] A few cases of perforating ulcer of the esophagus have been recorded.

HEMORRHAGE.

Aside from injuries, ulceration, etc., hemorrhage may take place from the lower veins of the esophagus, which, in obstructed circulation, espesially in atrophic cirrhosis, may be much dilated—*esophageal varices.*[3]

DILATATION.

Simple Cylindrical Dilatations of the esophagus are usually the result of long-continued stenosis of the esophagus or of the cardiac end of the stomach, although not nearly all the stenoses are followed by dilatation. These dilatations are formed at first immediately above the stenosis and then extend upward. Dilatation may occur below the stricture. Only in rare cases does the dilatation involve the whole length of the tube. The entire wall of the dilated portion of the esophagus is thickened, and there may be polypoid growths from the mucous membrane.

In rare cases there is symmetrical dilatation of part or of the whole of the esophagus without a stenosis or other discoverable cause. In these cases the dilatation is usually greatest near the middle of the esophagus and diminishes upward and downward, so that the esophagus has a fusiform shape. The dilatation may reach a very considerable degree, the walls of the esophagus may be thickened, and its mucous membrane may be covered with papillary outgrowths or ulcerated.

The Sacculated Dilatations of the esophagus are of two kinds: those due to pressure, and those due to traction.

[1] For a study of aberrant islets of gastric mucosa in the upper end of the esophagus, see *Schaffer, J.*, Virchows Arch., 1904, clxxvii, 181.

[2] For a study of rupture of esophagus, see *McWeeney*, Lancet, 1900, ii, 158 (bibl.).

[3] See *Preble, R. B.*, Am. Jour. Med. Sc., 1900, cxix, 263.

The dilatations due to pressure are situated in the posterior wall of the pharynx, just at its junction with the esophagus. The smaller sacs are from the size of a pea to that of a hazelnut; the larger sacs may reach a large size and hang down between the esophagus and the vertebral column, the opening into the esophagus remaining comparatively small. It is supposed that a limited area of the wall of the esophagus loses its power of resistance against the pressure exercised upon it in each act of swallowing; it then is forced outward by the pressure, and so there is formed first a protrusion and then a sac. When a sac is formed the food enters it, and accumulates there, and the sac becomes larger and larger.

The dilatations due to traction are situated on the anterior wall of the esophagus, at a point nearly corresponding to the bifurcation of the trachea. They are of funnel shape, with the small end outward. Their length varies from two to twelve millimeters; the width of the opening into the esophagus is from six to eight millimeters.

These dilatations are due to inflammation of the parts adjoining the esophagus, especially of the bronchial nodes, followed by adhesions to some part of the anterior wall of the esophagus. These adhesions then contract and draw the wall of the esophagus outward, and in this way the dilatations are formed.

At a later time these sacs may perforate into the bronchi, the lungs, the pleural cavity, the pericardium, the aorta, or the pulmonary artery.[1]

STENOSIS.

Congenital Stenosis.—Besides the defects of development of the esophagus which are incompatible with life, there may be a congenital stenosis of some part of it which causes difficulty in swallowing, but yet does not destroy life.

Compression Stenosis is not uncommon. Tumors of the neck and mediastinum, and aneurysms of the aorta are the usual causes. Stenosis from vertebral ecchondroses has been reported.[2]

Obstruction Stenosis.—Foreign bodies may be lodged in the esophagus. Tumors may hang down from the pharynx into the esophagus, or may be situated in the wall of the esophagus. Inflammation of the esophagus, due to the ingestion of irritating poisons, may induce cicatricial stenosis. A few cases of stenosis due to syphilitic inflammation have been reported.

INFLAMMATION. (Esophagitis.)

Catarrhal Esophagitis may be either acute or chronic. The chronic form may lead to ulceration, or relaxation and dilatation of the walls, or to hypertrophy of the muscular coat. Leukoplakia is not uncommon.

Pseudomembranous Esophagitis may occur with a similar process in the pharynx, with the exanthemata and other severe diseases, or under

[1] For bibl. of esophageal diverticula, see *Brosch*, Deutsch. Arch. f. klin. Med., 1900, lxvii, 44; and *Starck*, Arch. f. Verdauungskr., 1901, vii, 1. For later cases, see *Pfaff*, Tr. Assn. Am. Phys., 1901, xvi, 656.

[2] See *Zahn, H.*, München. med. Wchnschr., 1906, liii, 906.

other conditions. It may be diphtheritic in character or due to other excitants than the diphtheria bacillus.

Other Forms of Inflammation of the Esophagus.—Foreign bodies which are swallowed and become fixed in the esophagus may incite inflammation of the mucous membrane and of the adjoining soft parts. Abscesses may form around the esophagus, or destroy the wall of the canal, and the foreign body may find its way into the trachea, aorta, or pericardium.

Inflammation of the submucous tissue of the esophagus, apart from the cases just mentioned, is not common. It may result in abscess or the formation of fibrous tissue, causing stenosis.

Irritating and caustic acids and alkalies may destroy larger or smaller portions of the mucous membrane. The necrosed portions are of a black or whitish color, surrounded by a zone of intense congestion. If the patient recovers, the patches of membrane which have been destroyed slough and fall off, leaving a surface covered by granulation tissue. As this assumes cicatricial characters and contracts, serious stenosis of the esophagus may be produced.

Tuberculous Esophagitis may occur in generalized miliary tuberculosis or by local infection from tuberculous sputum, either with or without obvious predisposing local lesion, or through an extension of a tuberculous process from adjacent structures. Ulceration is apt to occur.[1]

Syphilitic Esophagitis.—There may be gummata which encroach upon the lumen, or ulceration followed by cicatrices may lead to stenosis.

TUMORS.

Small **papillomata** may occur singly or in considerable numbers throughout the entire length of the esophagus; large ones are more rare. Submucous **fibromata, lipomata, angiomata, myomata,**[2] **leiomyomata, rhabdomyomata,**[3] **fibromyomata,**[4] may develop in the esophagus. Mixed tumors[5] sometimes arise, and **adenomata** and **myxomata** have been observed.

As for malignant growths, **sarcomata** are rare.[6] **Carcinomata,** which are more common, may originate at any part of the wall of the pharynx and esophagus. The growth may encircle the tube; it may remain as a flat infiltration (Fig. 464), or may project inward in large fungous masses. In any case it is prone to ulceration. It may extend up and down the esophagus and involve even the pharynx or stomach; or the ulceration may extend outward and perforate into the air passages, lungs, pleura, pericardium, or large blood-vessels.[7] **Carcinosarcoma** sometimes involves the esophagus.[8]

[1] For bibliography of tuberculous esophagitis see *Flexner*, Bull. Johns Hopkins Hosp., 1893, iv, 4; and also *Cone*, ibid., 1897, viii, 229.

[2] *Itlig.*, Inaug.-Diss., Giessen, 1894 (abstr. in Centralbl. f. allg. Path., 1897, viii, 920); *Anitschkow*, Virchows Arch., 1911, ccv, 443 (bibl.).

[3] *Wolfensberger*, Zieglers Beitr., 1894, xv, 490 (bibl.).

[4] *Hall*, Quart. Jour. Med., 1916, ix, 409 (bibl.); *Anitschkow*, Virchows Arch., 1911, ccv, 443 (bibl.).

[5] *Glinski*, Virchows Arch., 1902, clxvii, 383 (bibl.).

[6] *v. Hacker*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1908, xix, 396 (bibl.); *Donath*, Virchows Arch., 1908, ccxiv, 446 (bibl.).

[7] For a résumé of tumors of the esophagus, see *Coplin*, Am. Med., 1904, vii, 773

[8] *Herxheimer*, Zieglers Beitr., 1908, xliv, 150 (bibl.); *Herzog*, Verhandl. d. deutsch. path. Gesellsch., 1914, xvii, 346 (bibl.); *Saltykow*, ibid., 351 (bibl.).

Cysts.—Small retention cysts of the follicles of the mucous membrane are sometimes found. Larger cysts lined with ciliated epithelium have been described.[1]

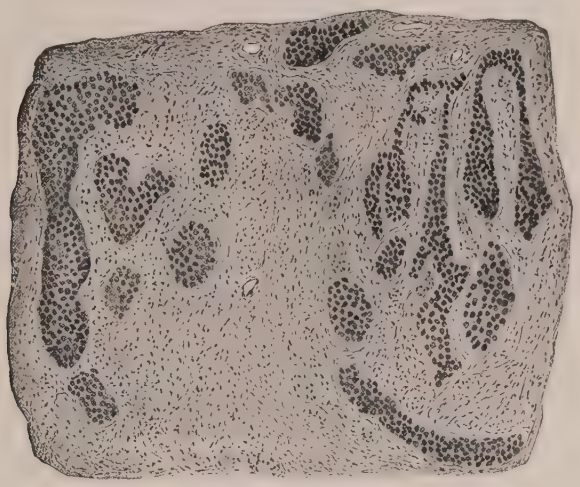


Fig. 464.—Infiltrating Carcinoma of the Esophagus.

The Stomach.

Malformations.

Malformations of the stomach are not common. The organ may be entirely wanting in acephalous fetuses. It may be of various degrees of smallness, sometimes no larger than the duodenum. It may be divided into two parts by a deep constriction in the middle. It may be vertically placed. Diverticula are noted. The stomach may be outside of the abdominal cavity from a hernial protrusion through the diaphragm or at some point in the abdominal wall. It is found on the right side, instead of the left, when the other viscera are transposed, and the position of the cardiac and pyloric orifices is correspondingly inverted.

Congenital stenosis of the pylorus in infants is of occasional occurrence. It is commonly due to hypertrophy of the muscular layers, which often involves the fibrous coats, also.[2]

Cadaveric Changes.

The mucous membrane of the stomach is liable to undergo considerable alterations soon after death, owing to changes in the distribution and composition of the blood and to the action of the digestive fluids. The blood is apt to collect in the small veins, especially at the fundus, while, by diffusion of the coloring matter, red or brown or black streaks and patches form in the mucous membrane.

Those portions of the mucosa on which the food and digestive fluids collect, usually at the fundus and on the posterior aspect of the stomach, frequently appear gray and turbid, and are soft and easily rubbed off. The epithelium in these regions is unusu-

[1] *Stoebe*, Zieglers Beitr., 1912, lii, 512 (bibl.); *Staehelin-Burckhardt*, Arch. f. Verdauungskr., 1909, xv, 584 (bibl.); *Pappenheimer*, Proc. New York Path. Soc., 1913, xiii, 60 (bibl.).

[2] See *Wachenheim, F. L.*, Am. Jour. Med. Sc., 1905, cxxix, 636; *Holt. L. E.*, Jour. Am. Med. Assn., 1917, lxviii, 1517 (bibl.); *Ibrahim, J.*, Ergebn. d. Med. u. Kinderheilk., 1908, i, 208 (bibl.) and *Strauss, A.*, Jour. Am. Med. Assn., 1918, lxxi, 807.

ally granular or disintegrated, and is often detached. Sometimes this post-mortem softening involves the entire thickness of the stomach wall, which is converted into a gray or yellow or brown gelatinous pulp. Thus large or small post-mortem perforations may occur.

INJURIES.

Perforating wounds of the stomach usually give rise to a fatal peritonitis. It is possible, however, for the wound to heal, or for a gastric fistula to form.

Rupture of the stomach may be produced by severe blows or falls. Minor degrees of injury may produce ulcer.

HEMORRHAGE. (Hematemesis.)

Small extravasations of blood in the wall of the stomach are frequently found in persons who have died from one of the infectious diseases.

Hemorrhage into the cavity of the stomach may occur in a variety of ways. It may take place from injuries or poisons; from ulcers or

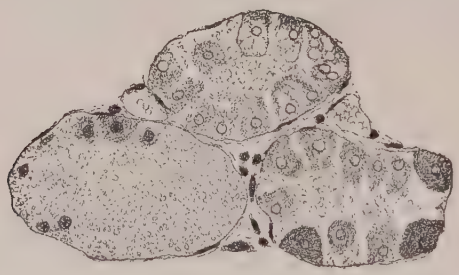


FIG. 465.—FATTY DEGENERATION OF THE EPITHELIUM OF THE GASTRIC TUBULES IN PHOSPHORUS POISONING.

carcinoma; from rupture of small aneurysms of the stomach, or from the rupture into the stomach of aneurysms elsewhere. It may occur in infectious diseases, especially in yellow fever, or in diseases of the blood. It may be associated with passive congestion of the stomach in hepatic cirrhosis of the liver, with obstruction of the portal vein, chronic disease of the heart and lung, an enlarged spleen, and chronic gastritis. In the new-born and in young infants hemorrhage into the stomach not infrequently occurs without apparent lesions which would account for it; or there may be ulcers of the mucous membranes, or cardiac disturbances, or infection. While the source of hemorrhage into the stomach is often evident, in many cases none can be discovered. Considerable bleeding can evidently take place by diapedesis from congested vessels.

Some cases of chronic gastritis are characterized by general bleeding from the mucous membranes of the stomach.[1]

[1] For a study of occult hemorrhage in the gastrointestinal canal, see *Jaworski* and *Korolewicz*, Wien. klin. Wchnschr., 1906, xix, 1129.

ATROPHY AND DEGENERATION.

Atrophy of the stomach occurs in a variety of cachectic conditions, in chronic inflammation, and in stenosis of the cardiac orifice.

Albuminous degeneration of the epithelium may occur in infectious diseases and in inflammation of the stomach.

Fatty degeneration is often associated with arsenic and phosphorus poisoning (Fig. 465).

Amyloid degeneration of the small vessels is associated with a similar process in other parts of the body.

INFLAMMATION. (Gastritis.)

Acute Catarrhal Gastritis is usually due to the ingestion of irritating decomposing or infectious substances and may accompany general infectious diseases.

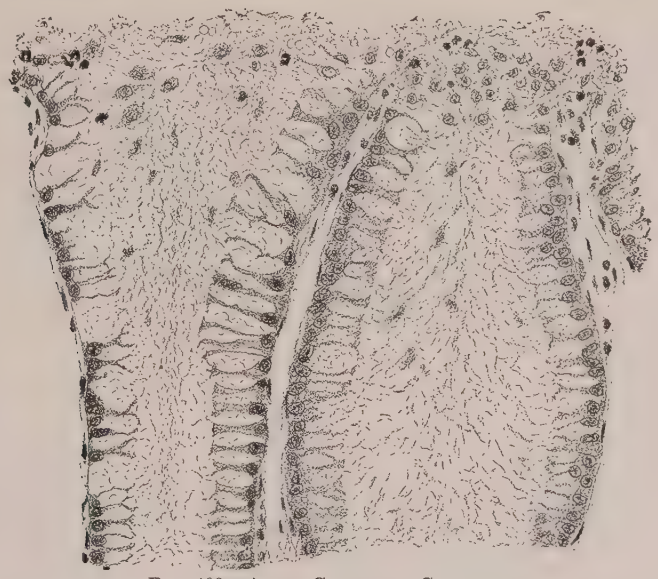


FIG. 466.—ACUTE CATARRHAL GASTRITIS.

Showing the open ends of two gastric tubules. There is a considerable formation of mucus by the epithelial cells, many of which have the so-called "beaker" form. There is exfoliation of epithelium which, with mucus and a few leucocytes and red blood-cells, covers the surface of the mucous membrane.

After death the mucous membrane may be congested and swollen, or the congestion may have disappeared. The mucous membrane is coated with an increased amount of mucus, especially at the pyloric end of the stomach.

The structural changes in the mucous membrane consist chiefly in swelling and albuminous degeneration, and sometimes exfoliation of the epithelium with an increase in the production of mucus by the cylindrical cells (Fig. 466), while the intertubular tissue and the submucosa may be

edematous and contain a few emigrated leucocytes. The solitary lymph-nodules may be enlarged from hyperplasia, and hemorrhagic erosions may be present.

Chronic Gastritis.—This, with the continuance of the exciting conditions, may follow the acute form. It is often associated with the persistent use of alcohol, with ulcers and carcinoma, with venous congestion from heart lesions, cirrhosis of the liver, obstruction of the portal vein or ascending vena cava, or chronic diffuse nephritis. These are doubtless predisposing conditions rather than actual excitants of the disease.

The stomach may be normal in size or small or dilated. Its inner surface is usually covered with tenacious mucus. The mucous membrane may be congested with minute hemorrhages or erosions, or it may be pale and gray or pigmented from former hemorrhages. It may be thickened or thinner than normal. Often, owing to irregular thickening, it projects in places in the form of minute granules, or it is irregularly

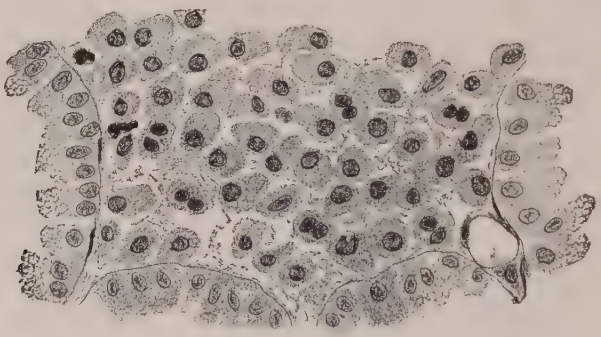


FIG. 467.—CHRONIC GASTRITIS.
Showing a small portion of the new-formed tissue between the gastric tubules. There are many large polyhedral cells in the new tissue.

roughened—*état mamelonné*—or there may be distinct polypoid outgrowths. These alterations are usually most marked in the pyloric region. Microscopical examination shows alterations varying in different parts of the organ and in different stages of the disease. The surface epithelium may be degenerated and exfoliated. The detached epithelium with leucocytes may be mingled with the mucus covering the surface. The gastric glands may be variously altered. They may be dilated, or elongated and tortuous, or hyperplastic[1] or atrophied; their epithelium may be flattened, degenerated, or detached. The interstitial tissue and the submucosa may be infiltrated with small spheroidal cells or new-formed larger polyhedral cells (Fig. 467), and new fibrous tissue may form (Fig. 468), thus often greatly thickening the mucous membrane and causing atrophy of the glands. The lymph-nodules at the base of the glands may be enlarged from hyperplasia. On the other hand, the mucous membrane, as contraction takes place in the new-formed intersti-

[1] See *Cone*, Welch Anniversary Contributions to the Science of Medicine, 1900, p. 877 (bibl.).

tial tissue, may undergo great atrophy (Fig. 469), so that it is pale, thin, often gray in color, with more or less pigmentation.

The formation of new fibrous tissue may later involve the muscularis also, leading to various distortions of the stomach.

A much more extensive form of chronic cirrhosis of the stomach (*linitis plastica*) is occasionally seen, in which there is a formation of dense connective tissue in the pyloric region or involving the entire organ, and causing a shrinkage of the whole viscus.[1] The affected portions are cartilaginous in texture. Microscopically, the sclerotic process is found mainly in the submucosa, but it may invade the muscularis and even the serosa. In the last instance, the disease usually affects more or less extensively all the serous membranes (*fibrous polyserositis*). It is sometimes

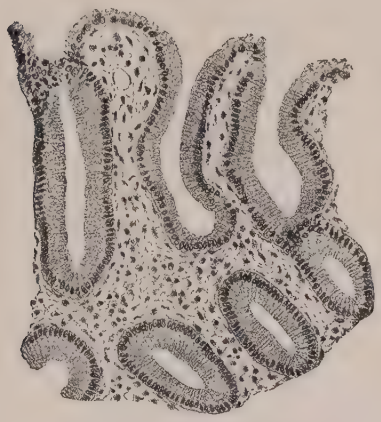


Fig. 468.—Chronic Gastritis.
Showing the new-formed fibrous tissue between the gastric tubules.

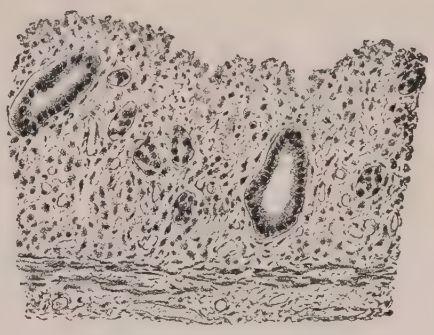


Fig. 469.—Chronic Gastritis.
Showing atrophy of the mucous membrane with much new-formed fibrous tissue.

difficult to distinguish linitis plastica from a scirrhous carcinoma of the stomach wall which does not involve the mucosa.

Croupous Gastritis (Membranous or Diphtheritic Gastritis).—This form of gastric inflammation, most common in children, may be associated with diphtheria or with other infectious diseases, but may occur independently. In adults it is usually secondary to typhus fever, pneumonia, pyemia, typhoid fever, the exanthemata, and other infections, or may follow the ingestion of irritant poisons. The excitants are thus of the most varied kinds, as is the case in pseudomembranous inflammation elsewhere in the body.

Exudative Gastritis (Suppurative or Phlegmonous Gastritis).—This process is characterized by the formation of purulent and other exudate in the connective tissue of the mucosa and submucosa. The exudate may be diffuse or localized in the form of abscess. As an independent affection it is rare. It is more frequent in connection with puerperal fever

[1] *Krompecher*, Zieglers Beitr., 1910, xlix, 384; *v. Sury*, Arch. f. Verdauungskr., 1907, xiii, 1. *Lyle, H. H. M.*, Linitis plastica (cirrhosis of stomach), Ann. Surg., 1911, liv., 625, complete bibl.

and other infectious diseases; it has been ascribed to injury and also to alcoholism.

The accumulation of exudate may be slight, the interglandular and submucous tissue being edematous with few pus cells. The mucous membrane may under these conditions remain intact or show slight catarrhal lesions. When this relatively slight accumulation of exudate occurs in the pyloric region it may apparently occasion temporary stenosis. On the other hand, a considerable or large amount of exudate may form, and the process may involve diffusely a large part of the wall of the stomach; or the process may be circumscribed and abscesses may form. The suppurative process may extend to the mucous membrane, or to the serosa, and thus perforations may occur with the incitement of peritonitis. Little is known of the direct excitants of phlegmonous gastritis.[1] Streptococcus pyogenes has been found in the exudate.[2]

Toxic Gastritis.—The mineral acids, the caustic alkalies, arsenic, corrosive sublimate, and the metallic salts, phosphorus, camphor, and other irritating materials, induce different lesions of the stomach, according to their quantity, their strength, and the length of time which has elapsed before death.

In large quantities they destroy and convert into a soft, blackened mass both the mucous membrane and the other coats, so that perforation may take place. In smaller quantities they produce black or white sloughs of the mucous membrane, surrounded by a zone of intense congestion. If death does not soon ensue, the ulcerative and cicatricial processes which follow such sloughs may contract and deform the stomach in various ways.

If the poisons are of less strength they may induce a diffuse congestion of the mucous membrane, with catarrhal or croupous exudation on its surface and serous infiltration of the submucous coat (see chapter on Poisons).

Tuberculous Inflammation of the stomach is rare and is usually secondary to tuberculous lesions elsewhere. There may be miliary tubercles or small or large, single or multiple ulcers involving especially the mucosa and submucosa.[3]

Syphilitic Inflammation of the stomach with ulceration has been occasionally observed.[4] The lesion is often not very characteristic as the changes due to the syphilitic poison are superimposed on those due to ulceration; but usually a few giant cells are present, and these with the perivascular infiltration, the absence of tubercle bacilli, and a positive Wassermann reaction permit of a diagnosis.

[1] Reference to the bibliography of microorganisms of the normal stomach may be found in an article by *Weiss*, Bacteria in the Stomach of the Cat, Jour. App. Microscopy, 1900, iii, 827; also *Coyon*, Flore microbienne de l'estomac, Thèse de Paris, 1900 (bibl.). For bibl. of phlegmonous gastritis, see *Leith*, Edinburgh Hospital Reports, 1896, iv, 51. For a later study, see *Schnarrwyler*, Arch. f. Verdauungskr., 1906, xii, 116 (bibl.).

[2] See *Kinnicutt, F.*, Tr. Assn. Am. Phys., 1900, xv, 127 (bibl.) For a study of lesions of the stomach as portals of entry of bacteria see *James*, Tr. Assn. Am. Phys., 1901, xvi, 72.

[3] For tuberculosis of the stomach, see *Dewey*, Jour. Infect. Dis., 1913, xii, 236; *Winternitz*, Bull. Johns Hopkins Hosp., 1908, xix, 223; *Pertik, O.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1902, viii[2], 273.

[4] Consult for bibliography, *Smithies, F.*, Jour. Am. Med. Assn., 1915, lxv, 572.

ULCERS OF THE STOMACH.

Simple or Peptic Ulcer.—This form of ulceration of the stomach is often seen. It occurs in males nearly three times as frequently as in females; and the peak of the age distribution, as shown by surgical material rather than by post-mortem statistics, is between twenty and thirty years, the average age for males being a trifle higher than that for females. The disease is almost unknown in children. Clinically, the ulcers are found in about 1 per cent. of general hospital admissions, and in about 4 per cent. of post-mortem examinations.[1]

They are most frequent on the posterior surface of the stomach, especially close to the pylorus and along the lesser curvature. On the anterior wall, the cardia, the fundus, and the greater curvature only a small percentage of ulcers occur.

In size they vary from one-quarter inch to five or six inches. They are usually of circular shape, but occasionally they are oval, and sometimes two or more ulcers fuse. The lesion is most extensive in the mucous membrane, and the ulcers may be confined to this or may extend outward, involving the connective tissue, and the muscular and, finally, even the peritoneal coats, the diameter becoming less as the ulcer progresses

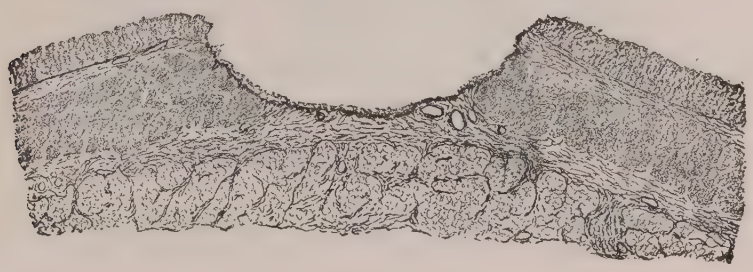


FIG. 470.—CHRONIC ULCER OF THE STOMACH.
Showing a section through the stomach wall at the central part of the round ulcer.

through the wall (Fig. 470). The ulcer looks like a clean hole punched out of the wall of the stomach (Fig. 471).

There are probably three different etiological factors in the production of ulcers of the stomach: (1) Some type of injury to the mucous membrane; (2) a disturbance of circulation; and (3) hyperacidity of the gastric juice. Nevertheless, the actual conditions underlying the production of simple ulcers are still obscure, though it seems probable that in some fashion the nutrition of a circumscribed portion of the wall of the stomach is interfered with and that then, and only then, is the mucous membrane of the wall destroyed by action of the gastric juice. But we are still ignorant of the way in which are produced the vascular changes which lead to the primary injury of nutrition. Nervous influences can apparently be excluded.[2] Gastric ulcer is frequently seen in chlorotic or

[1] *Welch, W. H.*, Pepper, System of Practical Medicine, 1885, iii, 504. Many important data are to be found in this excellent article.

[2] *Kawamura*, Deutsch. Ztschr. f. Chir., 1911, cix, 540 (bibl.). See, however, *Ophuls, W.*, Jour. Exper. Med., 1906, viii, 181.

anemic persons, and examination of the tissues about the ulcer often shows a good deal of vascular thickening and in some places a chronic obliterating endarteritis. Emboli have been found in branches of the gastric artery in cases of simple ulcer.

Recently, the possibility of a bacterial origin of the preliminary ischemic necrosis which permits of digestion of the mucous membrane by the gastric juice has been stressed, but the difficulties of producing such an ulceration with any constancy in the stomach of animals by any means has prevented a successful approach to the solution of the problem.[1]

There is usually but little active inflammatory change about the ulcer, though the edges are occasionally thickened by the growth of connective tissue. A moderate cellular infiltration is seen near the eroded surface. The mucous membrane of the remainder of the stomach is apt

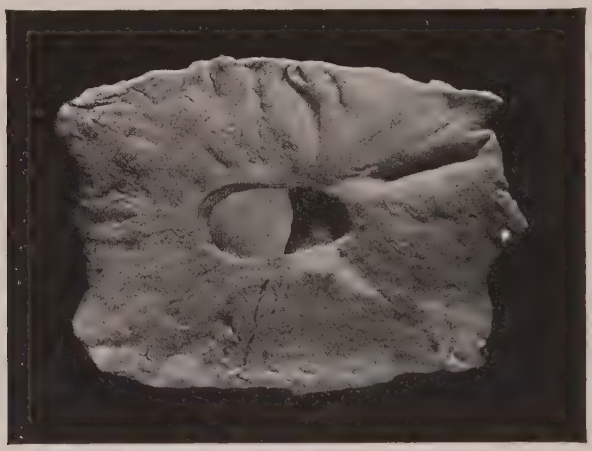


Fig. 471.—Chronic Perforating Ulcer of the Stomach.

to be in a condition of catarrhal inflammation. The ulcer may perforate directly through the wall of the stomach, the contents of the latter being discharged into the peritoneal cavity, and this may be the first evidence of the presence of the lesion. On the other hand, if the ulcer is more chronic dense adhesions may be formed between the wall of the stomach and the neighboring viscera, so that the bottom of the ulcer is closed and only a large tumor-like mass of inflammatory tissue is the result. Again, the liver, the intestine, and abdominal wall may adhere to the stomach, and these tissues be invaded by the ulcerative process, and cavities be formed which communicate with the lumen of the stomach. Local peritonitis and collections of pus may develop. Perforation may take place, also, into the duodenum or into the pericardial or pleural cavities. Repeated small hemorrhages occur regularly from the erosion of small

[1] For experimental production of gastric and duodenal ulcer, especially with reference to injections of bacteria, see *Rosenow, E. C.*, Jour. Infect. Dis., 1916, xix, 333 (good bibl.). See, also, *Steinharter, E. C.*, Boston Med. and Surg. Jour., 1917, clxxvi, 461; and *Celler, H. L.*, and *Thalhimer, W.*, Jour. Exper. Med., 1916, xxiii, 791.

blood-vessels on the surface of the ulcer. This blood may be vomited or passed in the stool and can almost always be detected by modern laboratory methods. If a larger vessel is eroded quantities of blood will be vomited or passed as a black tarry mass from the anus.

Occasionally, a gaping vessel of considerable caliber is found in the floor of a gastric ulcer during operation or at autopsy, but usually the blood seems to come from the capillaries rather than from the larger arterial trunks.

The ultimate course of such ulcers is unquestionably toward cicatrization with the final restoration of the mucous membrane. This is especially the case if the irritation of the ulcer by food is avoided either by placing the patient on a diet or by the performance of a gastroenterostomy. Such cicatrization may produce various deformities of the stomach by production of the dense connective tissue formed during the process of repair.[1]

A not infrequent alteration in the very chronic ulcers is the appearance in the edges of changes suggestive of carcinoma. Opinions are still at variance as to the interpretation and relative frequence of this occurrence, some observers thinking that as many as 60 to 70 per cent. of chronic ulcers in persons of advanced years show microscopical carcinomatous changes, while others believe that at a maximum 10 per cent. of ulcers may become malignant.[2] The question must be settled by the observation of surgical material, because at the time of autopsy it is difficult or impossible to differentiate an extensive ulcerated carcinoma from an ulcer with carcinomatous changes, and thus to determine whether or not the growth began primarily as an ulcer.

Follicular Ulcers, similar to those in the small intestine, are of occasional occurrence in the stomach. They are formed by the degenerative changes and necrosis in the solitary lymph-nodules of the stomach.

For **Tuberculous Ulcers,** see above.

Hemorrhagic Erosions occur as rounded spots or narrow streaks, formed by a loss of substance of the mucous membrane. The mucous membrane at these points may be congested, soft, and covered by small blood-clots. The destruction of the mucous membrane is usually superficial, but may involve its entire thickness. The internal surface of the stomach may be studded with these erosions. They give rise to repeated hemorrhages, and are accompanied by catarrhal inflammation of the rest of the mucous membrane.

They occur at all periods of life, even in infants. Their usual seat is the pyloric portion of the stomach. They may occur independently of other obvious lesions, but are most frequent in connection with chronic

[1] For general surveys of the subject, see *Martin, C. F.*, Osler and McCrae, Modern Medicine, 2d edition, Philadelphia, 1914, iii, 168; *Smithies, F.*, Cancer of the Stomach, Philadelphia, 1916; and *Versé*, Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 374.

[2] See *Hauser, G.*, Das chronische Magengeschwür, Leipzig, 1883; *Wilson, L. B.*, and *McDowell, I. E.*, Am. Jour. Med. Sc., 1914, cxlviii, 796; *Friedenwald, J.*, ibid., p. 660; *MacCarty, W. C.*, and *Broders, A. C.*, Arch. Int. Med., 1914, xiii, 208; *Mayo, W. J.*, Jour. Am. Med. Assn., 1915, lxv, 1069 (bibl.); *Ochsner, A. J.*, ibid., p. 1073; *Smithies, F.*, Cancer of the Stomach, Philadelphia, 1916; *Wilensky* and *Thalhimer*, Ann. Surg., 1918, lxvii, 215; *Ewing, J.*, Relation of gastric ulcer to cancer. Ann. Surg., 1918, lxvii, 715.

congestion of the mucosa, chronic gastritis, infectious diseases, and intoxications.

DILATATION AND DISPLACEMENT.

Very considerable degrees of dilatation of the stomach are found at autopsies usually in persons with enteroptosis, without stenosis of the pylorus or other mechanical cause to account for them. It is usually difficult to determine how long these dilatations have existed and their influence in the illness or death.

Acute dilatation of the stomach, with vomiting of very large quantities of thin fluid, has been observed in a few cases, the dilatation being developed suddenly and without discoverable cause.

Of the mechanical factors which lead to dilatation of the stomach a stenosis of the pylorus is the most common. Such a stenosis may be effected by a tumor, by chronic inflammation and thickening, and by the cicatrization of ulcers. Less frequently obstructions of the small and large intestines act in the same way. Postoperative dilatation is not infrequent, and is due in some instances to atony, in others to mechanical closure of the duodenum by direct pressure or indirectly by traction on the mesentery. Some forms of chronic gastritis are attended with dilatation of the stomach without stenosis. In rare cases circumscribed, sacculated dilatations are produced by the presence of foreign bodies—portions of wood, metal, etc.

The stomach may be variously displaced by pressure from without.

TUMORS.

Papillomata.—It has already been mentioned that some cases of chronic gastritis are accompanied by small polypoid hypertrophies of the mucous membrane; but besides these, polypoid tumors are found which may reach a considerable size and may number as many as two hundred.[1] They are composed of a connective tissue stroma arranged in tufts and covered with cylindrical epithelium. In some places tubules lined with cylindrical epithelium are found, so that the growth has partly the structure of an adenoma (Fig. 472).

Fibromata of small size are sometimes found in the connective tissue coat, and **lipomata** may develop in the same situation and assume the form of rounded or polypoid neoplasms. They usually project inward, but sometimes push outward beneath the peritoneum. **Leiomyomata** develop as rounded tumors in the muscular coat, but may gradually separate themselves from it and project either inward or outward.[2] The submucous **myomata** are at first small tumors lying loosely attached in the submucous coat, but as they grow larger they push the mucous membrane inward and become polypoid. Small multiple **angiomata** may be found in the stomach in connection with similar tumors in the sub-

[1] *Finney* and *Friedenwald*, Am. Jour. Med. Sc., 1917, cliv, 683 (bibl.); *Meulengracht*, Virchows Arch., 1913, ccxiv, 438.

[2] *James* and *Sappington*, Surg., Gynec., and Obst., 1915, xxi, 744 (bibl.).

mucosa throughout the gastrointestinal canal.[1] **Lymphomata** in the wall of the stomach are seen in some cases of leukemia and lymphosarcoma.

Sarcomata of the stomach are rare, though all types have been recorded.[2]

Adenoma.—Besides the papillomata discussed in a preceding paragraph, there are found in the submucous coat circumscribed tumors composed of tubules irregular in form and lined with one or more layers of cylindrical epithelium, like those of the gastric mucous membrane (see adenocarcinoma, below).

Carcinoma of the stomach is usually primary, though it may occasionally be metastatic. It may develop from polyps or adenoma,[3] though

FIG. 472.—SMALL PAPILLARY ADENOMA OF THE STOMACH.
This is confined to the mucous membrane, forming a small polypoid growth into the cavity. Enlarged about five diameters.

the origin from ulcer is much more frequent. It is of relatively common occurrence, the stomach in Welch's[4] analysis of over 30,000 cases being, next to the uterus, the organ most frequently affected. The common involvement of this structure shown in these figures is substantiated by more recent statistics;[5] thus, of a total of 52,420 deaths caused by cancer throughout the United States in 1914, 12,768, or about 24 per cent. were the result of cancer of the stomach.

[1] *Bennecke*, Virchows Arch., 1906, clxxiv, 171; *MacCallum*, Bull. Johns Hopkins Hosp., 1906, xvii, 258. For a review of the bibl. of benign growths of the stomach, see *Basch*, Surg., Gynec., and Obst., 1916, xxii, 165 (bibl.).

[2] *Dock*, Tr. Assn. Am. Phys., 1900, xv, 165 (bibl.); *Fenwick*, Lancet, 1901, i, 463 (bibl.); *Corner*, and *Fairbanks*, Practitioner, London, 1904, lxxii, 810; *Flebbe*, Frankfurt. Ztschr. f. Path., 1913, xii, 311 (bibl.); *Storch*, Deutsch. Ztschr. f. Chir., 1904, cxxviii, 218 (bibl.); *Hartz*, Surg., Gynec., and Obst., 1914, xviii, 502 (bibl.).

[3] *Versé*, Über d. Entstehung, d. Bau u. d. Wachstum d. Polypen, Adenome u. Karzinome des Magen-Darmkanals, Arb. a. d. path. Inst. z. Leipzig, 1908, Erster Band.

[4] *Welch*, Pepper's System of Practical Medicine, 1885, ii, 561.

[5] Mortality from Cancer and Other Malignant Tumors, Department of Commerce, Bureau of the Census, Sam. L. Rogers, Director, Washington, 1916, p. 15.

The situation of the tumor in Welch's summary of 1300 cases of carcinoma of the stomach was: pyloric region, 791; lesser curvature, 148; cardia, 104; posterior wall, 68; involving the greater part of the stomach, 61; greater curvature, 34; anterior wall, 30; fundus, 19; multiple tumors were found in 45 cases.

Carcinoma of the stomach is rare in childhood, though the physician must not lose sight of the fact that it may occur.[1]

Carcinomata of the stomach occur in various forms. There may be large or small, flat or rounded or lobulated growths projecting from the inner surface (Fig 473); the mucous membrane overlying them may be

FIG. 473.—CARCINOMA OF THE STOMACH. (Pyloric Region.)
A large globular tumor projects into the cavity.

intact or ulcerated; and the destructive process may advance far enough for the ragged or smooth-edged ulcers to reach a considerable size The wall of the stomach may be involved; peritoneal adhesions may form; or perforation may occur. On the other hand, carcinoma may assume the form of a diffuse infiltration of the stomach wall; growths of this type are less liable to ulcerate and are, indeed, often overlooked or mistaken for a chronic inflammatory lesion.

[1] *Osler* and *McCrae*, New York Med. Jour., 1900, lxxi, 581; *Brüning* and *Schwalbe*, Handbuch d. allg. Path. d. Kindesalters, Wiesbaden, 1912, p. 422 (bibl.).

Metastatic tumors are most common in the liver, lymph-nodes, and peritoneum, but may arise in any part of the body. Many neoplasms described in the earlier literature as primary carcinomata of the liver are now regarded as metastatic carcinoma from the stomach.

FIG. 474.—GELATINOUS CARCINOMA OF THE STOMACH.
Showing the infiltrating form of tumor occupying the pyloric end of the stomach and advancing along the wall.

The most common variety of carcinoma of the stomach is the *adenocarcinoma*, in which the glandular type is followed in many parts of the

growth (Fig. 261, page 461); cylindrical or polyhedral epithelial cells line variously shaped alveoli which frequently maintain well-marked lumina that are sometimes distended. Other portions of the growth, however, often show a medullary structure. It forms early and distant metastases.

Scirrhous carcinoma, the next most frequent type, is often of the infiltrating variety (Fig. 271, page 469). A third type, *gelatinous carcinoma*, frequently forms extensive growths and is also apt to invade adjacent structures and to establish metastases. *Squamous-cell carcinoma* of the stomach has been described.[1]

FIG. 475.—HAIR BALLS FROM HUMAN STOMACH.
This specimen consists largely of hairs, cotton and woolen threads, straws, etc.

Stenosis of the pylorus, chronic gastritis, adhesions, fistulæ, distortion, perforation, hemorrhage, and suppurative inflammation are among the most frequent secondary complications of gastric carcinoma. Of the relatively infrequent secondary cancers of the stomach, those originating in the breast are proportionately most numerous.[2]

Cysts of the stomach wall have been recorded.[3]

FOREIGN BODIES.

Among the various foreign bodies which by accident or design may be present in the stomach may be mentioned hairs, thread, string, etc., which have been swallowed from time to time, usually by hysterical

[1] *Borst*, Die Lehre v. d. Geschwülsten, Wiesbaden, 1902, p. 665; *Fütterer*, Jour. Am. Med. Assn., 1904, xliii, 1129.

[2] *Welch*, Pepper's System of Practical Medicine, 1885, ii, 561.

[3] *Schultze*, Proc. New York Path. Soc., 1899–00, p. 260.

For general bibl. of lesions of the stomach, see *Thorel*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 142.

For a study of retrograde metastases of carcinoma through the lymph-channels from the stomach to the liver, see *Jacob*, Arb. d. path.-anat. Inst., Tübingen, 1904, v, 121.

For general information, bibl., etc., pertaining to tumors of the stomach and intestine, see the monographs of *Borrmann*, Magencarcinoms, Mitt. a. d. Grenzgeb. d. Med. u. Chir., Erster Supplementband, Jena, 1910; *Hauser*, Das Cylinderepithel-Carcinom d. Magens u. d. Dickdarms, Jena, 1910; *Versé*, Über d. Entstehung, d. Bau u. d. Wachstum d. Polypen, Adenome u. Karzinome d. Magen-Darmkanals, Arb. a. d. path. Inst. z. Leipzig, 1908, Erster Band.

women. These may be closely packed together into a large mass nearly filling the cavity of the stomach, to which in shape it may correspond (Fig. 475).[1] Masses of shellac have been found in the stomachs of those who have satisfied their desire for alcohol by drinking varnish. Glass and metallic articles have been removed in large numbers from the stomachs of insane persons.[2]

The Intestines.

Malformations.

Atresia Ani.—Absence of the anal opening is frequent. This may be associated with partial or complete atresia of the rectum or of the colon, which may be represented by solid cords. Blind terminations of the small intestine may occur, or there may be complete closure of the gut. There may be absence of continuity between the large and small intestine.

The appendix may be absent, but this is a very rare anomaly.

Transposition.—The position of the intestines may be the opposite to that which is usually found. The transposition may affect all the abdominal viscera, or only a single viscus may be transposed.

Anomalous Positions.—The intestines with the other abdominal viscera may be partly without the abdominal cavity in failure of the abdominal walls to close in development (see Fig. 188, p. 369). Displacements of the colon are not infrequent.[3]

Diverticula.—*Congenital Diverticula.*—These are most frequent in the lower part of the ileum, occurring in about 1 per cent. of autopsies. They spring usually from the convex surface of the intestine, more rarely from the attached border, at a distance of about one meter from the ileocecal junction in adults. In the latter case they are joined to the mesentery by a fold of peritoneum. The diverticulum forms a pouch from two to fifteen cm. long, of about the same diameter as the intestine, smallest at its free extremity.

Fig. 476.—Diverticulum of the Small Intestine.

Such diverticula do not interfere with the functions of the intestines except in rare instances when the gut is stenosed.[4] They occasionally form part of a hernia. Sometimes the remains of these intestinal diverticula—called Meckel's diverticula—form soft, projecting tumors at the umbilicus[5] in children. Microscopical examination of such tumors often shows the structure of the intestinal mucosa and muscularis or even tissues resembling the pancreas at the tip.[6] If they remain attached by a fibrous cord to the navel, this cord may be the cause of incarceration of a portion of the intestines.[7]

[1] Such a specimen, mentioned by *Osler*, is in the museum of McGill University; another, reported by *Findler* (see Fig. 463), is in the museum of the College of Physicians and Surgeons, New York. See *Jacobson, N.*, Med. News, 1901, lxxviii, 245; *Fenwick*, Brit. Med. Jour., 1902, ii, 1696 (bibl.), *Heazlit, L.*, Jour. Am. Med. Assn., 1914, lxii, 107 (bibl.), *Matas, R.*, Surg., Gynec., and Obst., 1915, xxi, 594, and *O'Brien, F. W.*, Boston Med. and Surg. Jour., 1918, clxxviii, 396.

[2] See, for example, a case with 452 foreign bodies, *Eliason, E. L.*, Jour. Am. Med. Assn., 1917, lxix, 2106; and another with 95 hairpins, *Nix, J. T.*, ibid., 1917, lxviii, 840.

[3] For bibliography of reported cases, see *Shober, J. B.*, Am. Jour. Med. Sc., 1898, cxvi, 405.

[4] *Doepfner, K.*, Deutsch. Ztschr. f. klin. Chir., 1911, cix, 396.

[5] For bibliography of umbilical tumors, see *Giannettasio*, Arch. gén. de Méd., 1900, iii, 65; and *Cullen*, The Umbilicus and its Diseases, Philadelphia, 1916. For diverticula of duodenum, see *Davis*, Tr. Chicago Path. Soc., 1913, ix, 1.

[6] *Albrecht* and *Arzt*, Frankfurt. Ztschr. f. Path., 1910, iv, 167.

[7] For bibliography, see *Riesman*, Proc. Path. Soc., Philadelphia, 1898, N. S., i., 193. For case of volvulus of Meckel's diverticulum, see *Taylor*, Bull. Johns Hopkins Hosp., 1901, xii, 326. For a study of the diseases connected with Meckel's diverticulum, see *Griffith, J. P. C.*, Jour. Am. Med. Assn., 1914, xii, 1624 (bibl.).

Acquired Diverticula.—Not infrequently one finds at autopsies either in the small or large intestine diverticula or herniæ which project from the exterior of the gut, usually near its mesenteric attachment. These consist of the mucous membrane which has been crowded through the muscularis and is covered by serosa. They may form in connection with the appendix. These so-called "false diverticula" may be large, but are generally not larger than a pea; they may be single or numerous (Fig. 477). They as a rule cause no functional disturbance, but may, through the accumulation of fecal material within them, be the seat of perforation, inducing abscesses or peritonitis; or they may lead to local adhesion to adjacent parts.[1] Carcinoma may develop in such diverticula.

Cloacæ.—The rectum may open into the bladder, urethra, or vagina. Thus cloacæ are formed which are often associated with other malformations of the abdominal wall, intestines, and generative organs.

Incarceration, Volvulus.

1. The most common form is that in which a portion of intestine is strangulated by a fibrous band. Such fibrous bands are the result of peritonitis or may be of fetal origin. The intestine becomes in some way caught under one of these bands and is compressed by it. The stricture thus produced may lead to a gradual accumulation of feces in the intestine above it, and may last for a long time before death ensues. In other cases the stricture interferes at once with the circulation of the blood; the intes-

Fig. 477.—Multiple False Diverticula of the Intestine.

tine is intensely congested, becomes gangrenous, and death takes place with the symptoms of general peritonitis.

2. A portion of intestine becomes caught in some abnormal opening in the mesentery or omentum, or in the foramen of Winslow, or between the two layers of the mesentery. We have seen a case in which twelve feet of intestine had passed through a small opening in the mesentery.

3. A coil of intestine makes a half turn at its base, so that the two sides of the loops cross at its base. In this way the lumen of the intestine is completely closed and the vessels are compressed, so that congestion, peritonitis, and gangrene result. In the small intestine it may occur when the gut is fixed by old adhesions. This twisting of the gut is called *volvulus*.

4. A portion of the intestine, with its mesentery, makes one or more complete turns on itself, closing the canal and compressing the vessels.

5. A portion of the intestine makes a half or entire turn about its longer axis.

6. The mesentery of a part of the intestine is long and loose, in consequence of a dragging down of the intestine by a hernia or by habitual constipation. The portion

[1] Consult *Fischer, M. H.*, Jour. Exper. Med., 1901, v, 333 (bibl.); also *Beer, E.*, Am. Jour. Med. Sc., 1904, cxxviii, 135. For diverticula of appendix, see *Corning, E.*, Albany Med. Ann., 1905, xxvi, 816. For studies of acute diverticulitis, see *Rosenheim*, Ztschr. f. klin. Med., 1904, liv, 475; *v. Hansemann*, Virchows Arch., 1896, cxliv, 400; and the numerous publications from the Mayo Clinic, especially *Mayo, W. J.*, Jour. Am. Med. Assn., 1917, lxix, 781 (bibl.).

Fig. 478.—Acquired Diverticulitis of Sigmoid Flexure.

of intestine thus permitted to hang down is habitually filled with feces, and by its pressure on some other part of the intestine produces an incomplete stricture.

Intussusception.

This change of position consists in the invagination of one portion of intestine in another portion (Fig. 479). Usually this takes place in the direction of the peristaltic movements, from above downward; more rarely in the opposite direction.

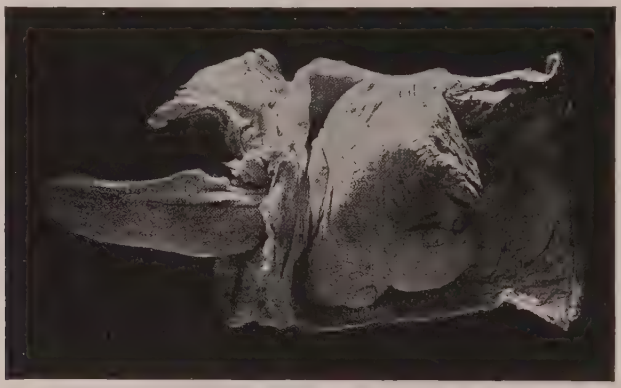


FIG. 479.—INTUSSUSCEPTION.
A portion of the gut is completely invaginated in the segment below and strangulated.

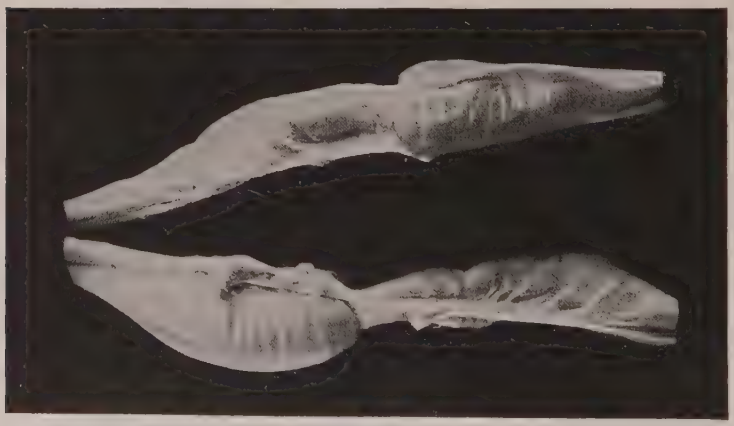


FIG. 480.—INTUSSUSCEPTION—AGONAL OR POST-MORTEM IN INTESTINE OF INFANT.

The parts are found in the following condition: There are three portions of intestine, one within the other. The inner portion is continuous with the intestine above the intussusception; its peritoneal coat faces outward. The outer portion is continuous with the intestine below; its peritoneal coat also faces outward. The inner portion is turned inside out, its mucous membrane is in contact with the mucous membrane of the outer portion. In rare cases the intussusception is complicated by the invagination of a second portion of intestine in the inner tube, and even by a third intussusception into the second one. These changes occur both in the large and small intestine; most frequently the lower part of the ileum is invaginated in the colon. The invaginated

portion may be from a few inches to several feet in length. The lesion is most frequently found in early childhood.

The intussusception, by the dragging and folding of the mesentery which it involves, may lead to intense congestion of the parts, and even to large hemorrhages between the coats of the intestine. The congestion may induce fatal peritonitis, or gangrene of the intestine, or chronic inflammation and adhesions, and the patient may live for a considerable time with symptoms of stricture. In other cases the invaginated portion of the intestine sloughs, the outer and inner portions become adherent, and the patient recovers, with or without stricture.

Besides this grave form of intussusception we often find, especially in children, one or more small invaginations not attended with congestion or inflammation. These are agonal or are formed immediately after death (Fig. 480).

FIG. 481.—INGUINAL HERNIA—INTESTINAL.

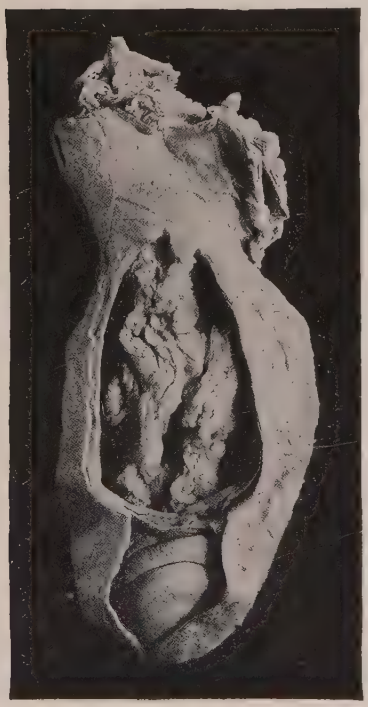


FIG. 482.—INGUINAL HERNIA—OMENTAL.

Hernia.

The dislocation and protrusion of the whole or a part of an internal organ from its normal position is called hernia. This may occur in various parts of the body, but most frequently involves the abdominal viscera, especially the intestine or omentum. In the most common form of the so-called inguinal hernia, which is of frequent occurrence in men, there is a descent into the inguinal canal of either a loop of intestine (Fig. 481) or a portion of the omentum (Fig. 482). For a description of the various forms of hernia we refer to works on surgery.

DILATATION OF THE COLON.

This may be congenital or acquired and is sometimes so extensive as to fill the abdominal cavity.[1]

A special type of enlargement of the colon, seen chiefly in children, bears the name *Hirschsprung's disease.*[2] The large intestine is enormously increased in diameter with extreme thickening of the wall, this thickening being greater the longer the disease has existed. The sigmoid flexure is long, but usually escapes dilatation, though children who survive to adolescence may show dilatation of the small intestine and stomach, also, with thickening of the walls. Muscular hypertrophy is responsible for the increase in the mural dimensions, the mucous and serous coats showing little or no change. The etiology of the condition is still obscure, but it is generally assumed that it is due to obstruction based on a congenitally abnormal length of the sigmoid flexure in consequence of which the coils of the gut are more numerous than normal and a certain amount of kinking may occur with consequent partial obstruction.

WOUNDS—RUPTURES.

Penetrating wounds of the intestine usually prove rapidly fatal, either from shock or from peritonitis. Sometimes, however, the wound becomes closed by the formation of adhesions with the neighboring parts. Sometimes the wound in the intestines becomes adherent at the position of the wound in the abdominal wall, and an intestinal fistula is formed.

Rupture of the small intestine is not infrequently produced by severe blows on the anterior abdominal wall. It is noticeable that such blows may not produce marks or ecchymoses of the skin. Such ruptures usually prove fatal very soon, but sometimes the patient lives several days and the edges of the rupture undergo inflammatory changes.

Strictures of the intestine are sometimes followed by rupture of the dilated intestine at some point above the stricture.[3]

DISTURBANCES OF THE CIRCULATION—HEMORRHAGE.

Hyperemia of the intestine may be inflammatory in character or it may be associated with disturbance of the portal circulation. Under both of these conditions ecchymoses may occur. Pigmentation may follow large or small interstitial hemorrhages.

As a result of **embolism** or **thrombosis** of the mesenteric vessels **hemorrhagic infarctions** may occur, sometimes involving a considerable portion of the gut.[4] Hemorrhage into the lumen may follow, or gangrene, or inflammation. The latter processes are readily induced in the injured regions by the bacteria constantly present in the intestinal contents. Septic emboli may induce suppurative inflammation in the mesentery and in the wall of the intestine.

[1] *Fitz, R.*, Am. Jour. Med. Sc., 1899, cxviii, 125 (bibl.); *Griffith, J. P. C.*, ibid., p. 283; *Hubbard*, Ann. Surg., 1916, lxiii, 349.

[2] *Puls*, Beitr. z. klin. Chir. (Bruns), 1910, lxix, 306; *De Jong* and *Muskens*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909–10, xxi, 647; *Konjetzny*, Beitr. z. klin. Chir. (Bruns), 1911, lxxiii, 155; *Cadwallader, R.*, Arch. Pediat., 1916, xxxiii, 665; *Heller*, München. med. Wchnschr., 1911, lviii, 1059.

[3] See summary of cases by *Gallaverdin, L.*, Gaz. d. hôp., 1901, lxxiv, 929, 956 (bibl.).

[4] For a further consideration of thrombosis of the mesenteric veins, consult *Welch*, Allbutt's System of Medicine, 1909, vi, 218. See, also, study by *Jackson, Porter*, and *Quinby*, Jour. Am. Med. Assn., 1904, xlii, 1469.

Intestinal **hemorrhage** may occur in venous congestion, as in certain forms of cirrhosis of the liver. It may follow ulceration in typhoid fever, in chronic colitis, in malignant tumors, etc.; it may accompany infarction.[1]

DEGENERATION.

Amyloid degeneration may be associated with a similar process elsewhere in the body. The iodine test may reveal the existence of this alteration in the villi of the small intestine.

INFLAMMATION.

Inflammation of the Small Intestine. (*Enteritis.*)

Acute Catarrhal Enteritis.—This may occur under conditions similar to those inciting catarrhal inflammation in the stomach. It may be local or general and may be associated with similar processes in the stomach and colon. In "ptomaine poisoning" the lesions are often severe. Comparatively mild forms of the lesion may predispose the intestine to the incursions of intestinal bacteria and the development of more severe forms of destructive lesions. The mucosa may be reddened or ecchymosed, and covered with mucus mingled with degenerated epithelium and leucocytes. The epithelium may be degenerated and peeled off (Fig. 483), and the cylindrical cells may be distended with mucus formed within them—"beaker cells."

Fig. 483.—Acute Catarrhal Enteritis.

Showing the open end of one of the tubular glands with exfoliating and disintegrating epithelium.

The solitary and agminated lymph-nodules may be swollen from hyperplasia. When this hyperplasia is marked (Fig. 484), the lesion is often called *follicular* or *nodular* enteritis, and erosions and ulceration may occur (Fig. 492 and 493).[2] This lesion is especially common in children suffering from various types of acute infection. For hyperplasia of the lymphoid tissue of the intestine in typhoid fever see page 272.

Chronic Catarrhal Enteritis.—This may follow the acute form or occur independently. It often accompanies many forms of chronic disease of the heart, kidneys, lungs, etc. The mucous membrane may be covered with mucus; ecchymoses, erosions, and pigmentation are frequent. There is hyperplasia of the inter-

[1] For reference to occult hemorrhage in gastrointestinal canal, see *Jaworski* and *Korolewicz*, Wien. klin. Wchnschr., 1906, xix, 1129.

[2] It is better to abandon the name nodular enteritis for this lesion and call it *nodular hyperplasia*.

glandular tissue of the mucosa and the submucosa. In this way there may be atrophy of the glands, and the mucous membrane may be thin and fibrous. The muscularis may also be involved and atrophied. The submucosa and the muscular layer may, on the other hand, be thickened from the new-formed fibrous tissue.

Pseudomembranous Enteritis may occur in connection with a similar condition in the colon, in infectious diseases, in chronic diseases of the

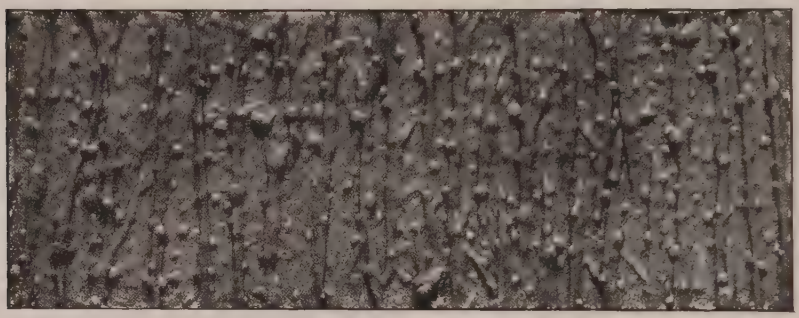


FIG. 484.—NODULAR HYPERPLASIA.
From the intestine of a child.

liver and kidney; in cachectic conditions, or as the result of the ingestion of irritant poisons. The mucous membrane may be the seat of superficial necroses, sometimes in patches, and the pellicle may consist largely of mucus with necrotic epithelium. Fibrin may be present, and fibrin and extravasated leucocytes and serous fluid may infiltrate the submucosa.

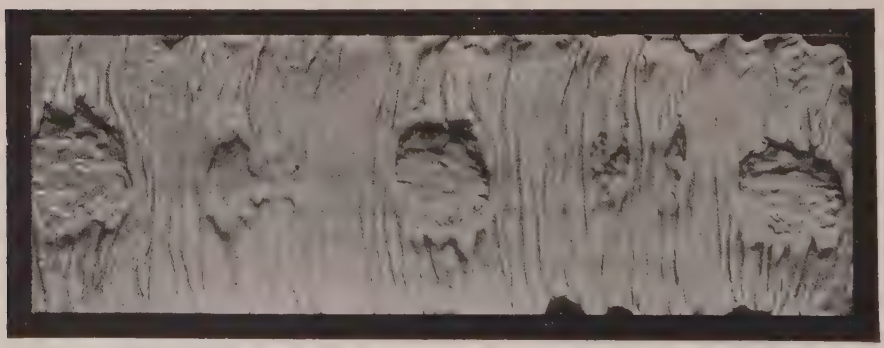


FIG. 485.—TUBERCULOUS ULCERS OF THE SMALL INTESTINE.
In the larger ulcers the mucous membrane is almost entirely gone, leaving the muscularis exposed at the bottom.

Exudative or Suppurative Enteritis is rare. Purulent foci, usually metastatic in origin, may form in the wall of the intestine. A more diffuse suppuration may follow infection after obstruction or strangulation.[1]

Tuberculous Enteritis.—The lymph-nodules and Peyer's patches are

[1] See for a study of phlegmonous enteritis, *MacCallum*, Bull. Johns Hopkins Hosp., 1906, xvii, 254 (bibl.).

often involved in intestinal tuberculosis and may ulcerate (Fig. 485). Miliary tubercles may be present with cheesy degeneration (Fig. 486) and the subperitoneal lymphatic vessels are often involved and may appear as white, nodular, branching, slightly elevated cords, running around the gut (Fig. 487). Tuberculous ulcers are apt to extend most rapidly in a direction transverse to the axis of the gut (Fig. 488), differing in this

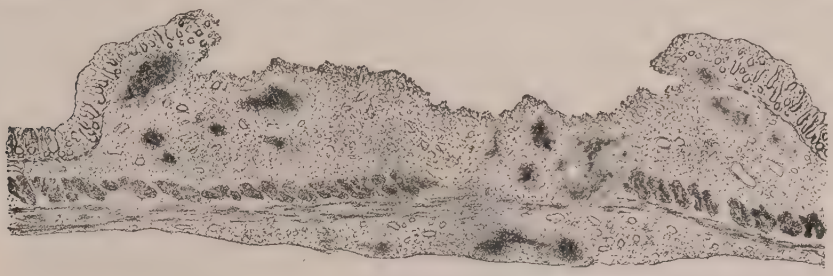


FIG. 486.—SECTION OF A TUBERCULOUS ULCER OF THE SMALL INTESTINE.
Showing tubercle tissue with miliary tubercles and caseation at the bottom of the ulcer. There are miliary tubercles beneath the serosa. (See Fig. 487.)

respect from typhoid ulcers (page 273). But to this there are frequent exceptions. Tuberculous ulcers rarely perforate. (See for other forms of tuberculosis of the intestine page 786).[1]

The mesenteric lymph-nodes are frequently involved in either active or inactive tuberculosis in any part of the body. They may not show

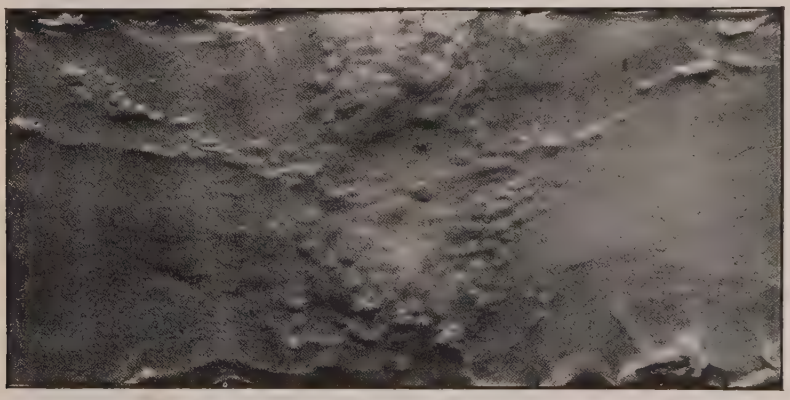


FIG. 487.—SUBSEROUS TUBERCLES FOLLOWING THE LYMPH-VESSELS AT THE BOTTOM OF A TUBERCULOUS ULCER OF THE SMALL INTESTINE.

gross lesions, but microscopically characteristic lesions or tubercle bacilli may be found. Frequently, when neither lesions nor bacilli are demonstrable, inoculation of guinea-pigs shows that the nodes are infected.

[1] For statistics of intestinal tuberculosis see *Zahn, F. W.*, München. med. Wchnschr., 1902, xlix, 49; *Nebelthau*, ibid., 1903, l, 1246, 1300; *Wagener*, ibid., 1903, l, 2036, 1095; and *Ipsen, J.*, Berl. klin. Wchnschr., 1906, xliii, 791. For presence of tubercle bacilli in mesenteric lymph-nodes, see *MacFadyen* and *MacConkey*, Brit. Med. Jour., 1903, ii, 129.

The mesenteric nodes are frequently infected without other tuberculous lesions in the body.[1] The bovine type of bacillus is often present.

Syphilitic Ulcers, originating in the lymphatic structures, are sometimes found in infantile syphilis.[2]

Duodenal ulcers, while usually simple, may be tuberculous; it has been stated that they may follow extensive burns, but apparently this is often only a coincidence.[3] They may occur under a variety of other conditions, and are much more frequent than was at one time supposed.[4] Carcinoma almost never develops on a duodenal ulcer. The sex distribution is the same as in the case of gastric ulcer, that is, the lesion is about three times as frequent in males as in females.[5]

Other Forms of Ulcers.—The solitary and agminated lymph-nodules frequently undergo hyperplasia in infectious diseases, after extensive

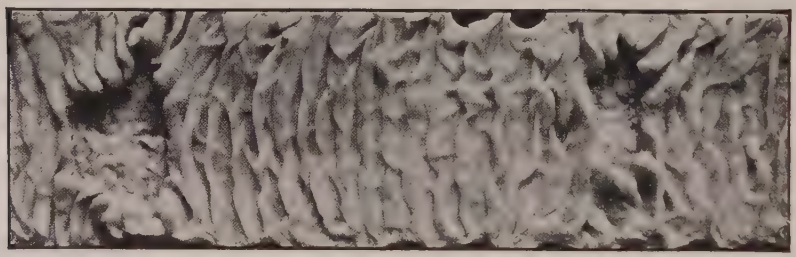


Fig. 488.—Tuberculous Ulcers of the Small Intestine.
Showing the extension of the ulcers in a direction transverse to the axis of the gut.

burns,[6] and in various forms of inflammation of the intestine. Hyperplasia of the lymphatic tissue—see page 775—with ulceration is especially frequent in children.

Inflammation of the Large Intestine. (*Colitis.*)

The mucous membrane of the large intestine is frequently the seat of acute and chronic inflammatory and necrotic processes known clinically as *dysentery.*[7] The rectum is most often involved, but sometimes the upper part of the colon and sometimes the whole colon is affected.

Acute Catarrhal Colitis.—This process is frequently limited to the lower end of the colon and presents several types. There may be an

[1] See *Rosenberger, R.*, Am. Jour. Med. Sc., 1905, cxxx, 95. For discussion of intestines as portals of entry of tubercle bacilli, see pp. 303 and 712.

[2] For study of acquired syphilitic ulcers of intestine, see *Arken*, Tr. Chicago Path. Soc., 1912, viii 224.

[3] *Busse*, Verhandl. d. deutsch. path. Gesellsch., 1914, xvii, 290.

[4] *Mayo, W. J.*, Ann. Surg., 1911, liv, 313, 427; *Moynihan, Sir Berkeley*, Brit. Med. Jour., 1912, i, 346; *Melchior, E.*, Ergebn. d. Chir., 1911, ii, 290.

[5] For a study of duodenal ulcers, see *Weir*, Med. Record, 1900, lvii, 749 (bibl.); *Gruber*, Mitt. a. d. Grenzgeb. d. med. u. Chir., 1912, xxv, 465; and *Moynihan, Sir Berkeley*, Duodenal Ulcer, Philadelphia, 1910.

[6] *Bardeen, C. R.*, Jour. Exper. Med., 1897, ii, 501.

[7] The classification of these lesions is with our present knowledge unsatisfactory, and is largely based upon morphology. In some phases of so-called dysentery—infectious colitis—however, the nature of the excitant is taken into the account. Consult for a special study of forms of colitis seen in New York, *Delafield*, Am. Jour. Med. Sc., 1897, cxiv, 401.

increased production of mucus, which coats the surface of the mucous membrane and is mixed with exfoliated and fatty or disintegrated epithelium and red blood-cells. The surface epithelium may be degenerated and exfoliate, many "beaker cells" being present, indicating the source of over-production of mucus (Fig. 489). The mucous membrane may be congested and infiltrated with serum and leucocytes. Again, with conditions similar to those just described, there may be a purulent exudate in the mucous membrane. There is a form of catarrhal colitis in which there is a more or less extensive formation of new connective tissue between the glands and in the submucosa. Finally, there may be small or extensive ulceration in the involved areas of the mucosa.

FIG. 489.—ACUTE CATARRHAL COLITIS.

The epithelium of the tubular glands, especially near their mouths, is forming an excessive amount of mucus with destruction and exfoliation of the cells. The tubules are dilated with mucus which covers the surface. The mucosa at the right is necrotic and forms the edge of an ulcerated area.

Acute Infectious Colitis (Tropical Dysentery) is of especially frequent occurrence in warm countries and is often epidemic. In one group of cases (*a*) the disease is probably incited by protozoa—Entamœba histolytica; while in the other (*b*), bacteria, some apparently related to the typhoid-colon bacillus group, and possibly others, are believed to be the excitants.

(*a*) AMEBIC COLITIS.—This form of colitis is apparently incited by the presence of the wall in the intestine of the Entamœba histolytica.

The amebas are found in the gelatinous masses which are common in the stools. They are of rounded shape, and, when alive, change their position and shoot out and retract little projections (pseudopodia). Their outer portion is composed of a pale hyaline or homogeneous substance; the inner contains vacuoles and is more refractive (see Fig. 78).

In the colon the amebas are found in the connective-tissue coat (Fig. 490) and in the floors of the ulcers.

Ameba excites at first a moderate exudative and productive inflammation followed by necrosis. Thus ulcers are formed. The ulcers may be superficial or deep, sometimes extending to the peritoneum; they enlarge by infiltration and necrosis at their edges, so that extensive destruction of the mucous membrane may occur. The amebas may be present in the connective tissue at the base or sides of the ulcers. Not infrequently, owing to bacterial infection from the intestinal contents, varying degrees of suppurative inflammation may complicate the lesion.

Necrotic and suppurative processes may be set up in the liver (see page 833) and in the right lung, and in these lesions the ameba may be found.[1] In the later stages, the amebas may disappear from the liver

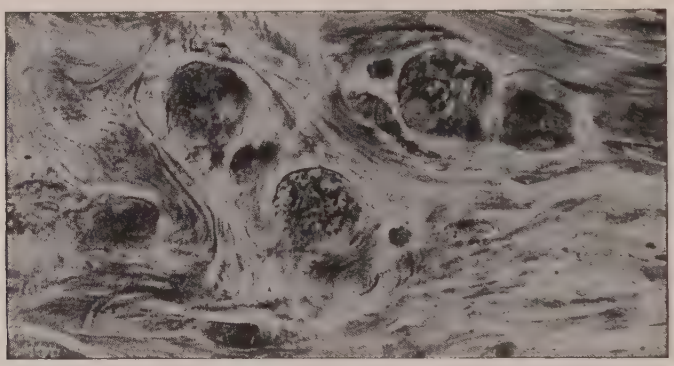


FIG. 490.—AMEBIC COLITIS.
Showing amebas in the submucous fibrous tissue.

abscesses, and a partial cure be effected by inspissation of the pus and dense connective tissue formation about the abscesses.

(*b*) ACUTE INFECTIOUS COLITIS WITH BACTERIAL EXCITANTS.—Another type of acute infectious colitis or dysentery occurs epidemically, especially in hot climates, and is most often seen among soldiers under war-time conditions, and in children during the hot weather. There is also a sporadic form which may occur at any time in temperate or hot climates. The lesions are variable. In the acute diarrheas of infants, congestion of the intestine and swelling of the follicles may be all that is found post mortem. Usually there is a small amount of blood mixed with thick mucus which covers the surface of the intestinal mucosa. The more severe types, especially in adults, show a pseudomembranous or ulcerative colitis, varying according to the extent and duration of the infection. Abscess of the liver, so frequently seen in the amebic type, is rare in the bacillary form. In the milder cases the process may be confined to the mucous membrane; in the more severe the inflammatory lesions involve the submucosa which may show extensive edema with

[1] See, for details and bibliography, *Kartulis*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d edition, 1913, vii, 651.

hemorrhages and, in the later stages, ulceration extending down to the muscular coats. In the chronic stage, the whole coat is thickened and dark in color from blood pigment deposited in the cells, and microscopical examination shows that the epithelium has largely disappeared and that only a few glands of the original mucous membrane are left. A large amount of connective tissue is found in the submucous and muscular coats.

The disease is due to a group of bacilli (page 283) whose differentiation depends upon fermentation reactions. The bacilli are found only in the intestines, and do not invade the rest of the body. The disease is unquestionably spread by carriers, those who are suffering from mild forms of infection, as well as those who are convalescent or healthy. In treatment excellent results have been obtained by the use of polyvalent antitoxic sera.[1]

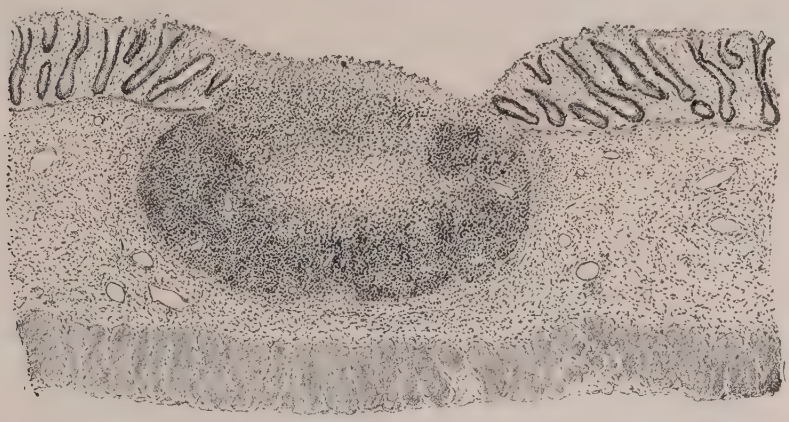


FIG. 491.—NODULAR COLITIS—FOLLICULAR COLITIS.
Showing commencing necrosis of the mucosa over the hyperplastic lymph-nodule.

Bacillus pyocyaneus has been repeatedly found in the discharges in cases of dysentery as well as in other intestinal disorders under conditions which justify the conjecture that it is sometimes, at least, an excitant of intestinal inflammation and necrosis. Streptococcus pyogenes has been repeatedly found in association with enteritis and colitis. Intestinal infection with streptococcus is more frequent and significant in children than in adults.[2]

Nodular Hyperplasia.—In many cases of catarrhal and croupous inflammation of the colon and of acute infections, especially in children, the solitary follicles (lymph-nodules) become more or less swollen and necrotic. Besides these cases, however, there are others in which the

[1] An excellent review of the bacteriology, clincial course, and lesions of the disease will be found in a monograph by *Ruge, R.*, Mense, Handbuch der Tropenkrankheiten, 2d edition, Leipzig, 1914, iii, 158.

For a general statement of forms and lesions of dysentery and its relationship to microorganisms, see *Flexner, S.*, Philadelphia Med. Jour., 1900, vi, 414; see also *Lentz*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d edition, 1913, iii, 899.

For a study of experimental colitis, see *Flexner* and *Sweet*, Jour. Exper. Med., 1906, viii, 514.

[2] See *v. Lingelsheim*, Kolle and Wassermann, Handbuch d. path. Mikroorganismen, 2d edition, 1912, iv, 451.

changes in the nodules form the principal part of the lesion, while the catarrhal or croupous inflammation is but slightly developed. The lesion is similar to that in nodular hyperplasia in the small intestine. The nodules are first swollen—hyperplastic—(Fig. 491), then necrotic, then slough away and leave little circular ulcers with overhanging edges (Fig. 492). These ulcers are usually numerous (Fig. 493) and

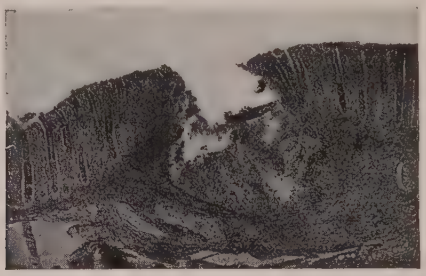


Fig. 492.—Nodular Colitis with Ulceration.
Showing necrosis and ulceration of the lymph-nodule with opening into the lumen of the gut.

may be scattered over a large part of the colon. The ulcers are apt to show but little disposition to heal, and the acute colitis often becomes chronic.

Nodular Colitis.—In rare cases of typhoid fever and occasionally under other conditions there are foci of inflammation with necrosis and ulceration irregularly scattered and involving primarily not the mucous membrane but the underlying tissue. These lesions are not to be iden-

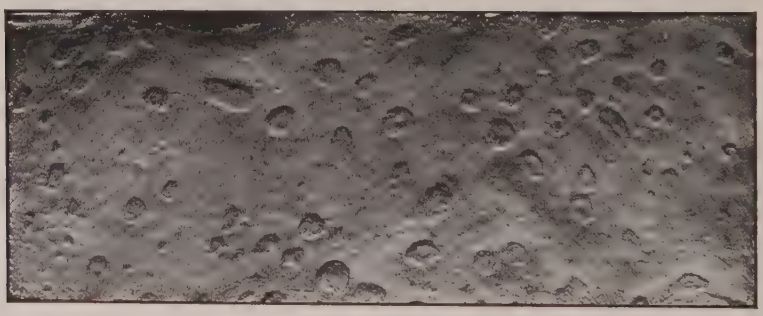


Fig. 493.—Nodular Colitis.
From the intestine of a child, showing numerous ulcers involving solitary nodules. (Compare Fig. 484.)

tified with hyperplasiæ of the solitary lymph-nodules with ulcerations which occur with especial frequency in children suffering from acute infections.[1]

Pseudomembranous (Croupous) Colitis.—This form of inflammation may involve the rectum alone, or the entire length of the colon, or only its upper portion. The mucous membrane is congested and swollen, and coated with a layer of false membrane; the connective tissue between and

[1] See *Whipple*, Bull. Johns Hopkins Hosp., 1906, xvii, 281.

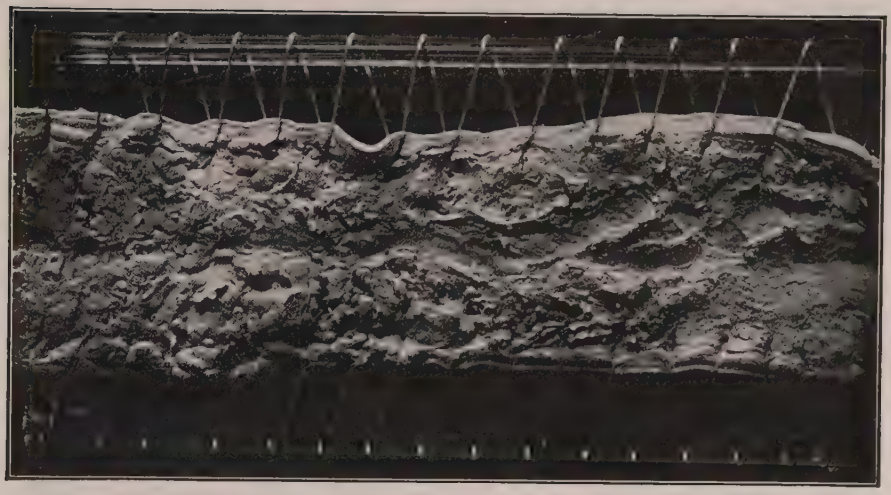


FIG. 494.—PSEUDOMEMBRANOUS (CROUPOUS) COLITIS.

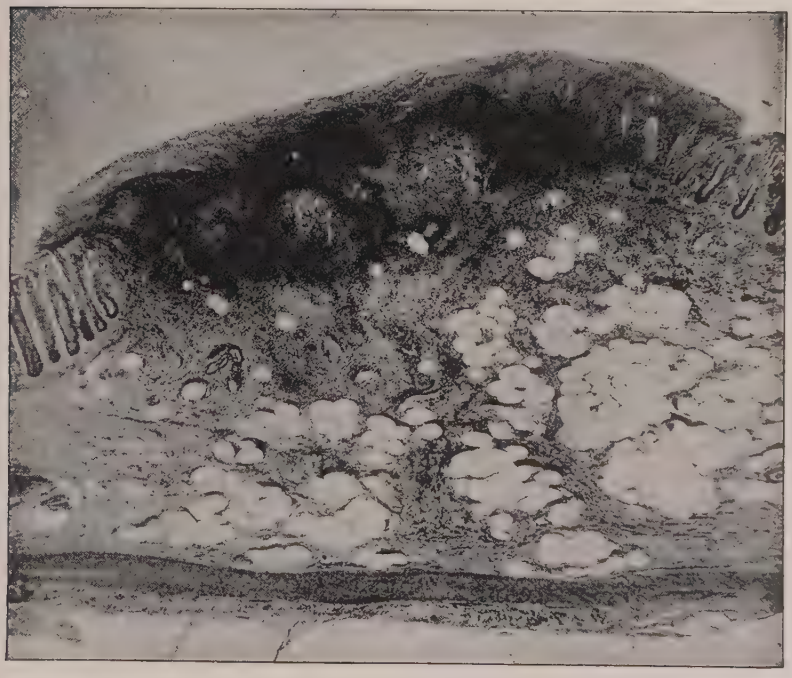


FIG. 495.—NECROTIC COLITIS.
Circumscribed congestion and necrosis of the glandular and connective-tissue coats.

beneath the gland tubules is infiltrated with fibrin and pus, and in severe cases the inflammation involves the muscular and peritoneal coats also. The inflammation is usually more intense at some places than at others, so that the surface of the mucous membrane shows the false membrane in isolated patches (Fig. 494). Less frequently there is a uniform coating with the false membrane. In mild cases, as the inflammation subsides, the products of inflammation are absorbed and the wall of the intestine returns to its normal condition. In more severe cases the quantity of the inflammatory products is so great that portions of the wall of the intestine become necrotic. This necrosis may involve only the glandular coat, or it may extend deeper into the wall of the intestine. The necrosed tissue after a time sloughs away, leaving behind ulcers of different sizes and depths. After this the ulcers may cicatrize, or their floors and walls may remain in the condition of granulation tissue for an indefinite length of time. When the latter is the case there is added a chronic inflammation of the wall of the intestine between the ulcers, with changes in the mucous membrane and thickening of the connective-tissue and muscular coats. This form of colitis is observed after bacterial invasion, following the ingestion of mercuric chloride,[1] and as a terminal condition in nephritis.

Fig. 496.—Chronic Ulcerative Colitis—Dysentery.
There are small erosions of the swollen mucous membrane.

Necrotic Colitis.—There is a form of inflammation of the colon in which considerable areas of the connective-tissue coat become necrotic, leaving the glandular coat undermined and separated from the muscular coat. In this way large ulcers with overhanging edges are developed. This form of colitis is very often fatal.

There is another very serious and obscure form of necrotic colitis which appears to be septic in character. After death the inner surface of the colon is found studded with little blackish areas in which the blood-vessels are gorged with blood. The glandular and connective-tissue coats are infiltrated with pus cells and there is a superficial necrosis (Fig. 495).

Various forms of microorganisms have been found in connection with

[1] *Weiler, F.*, Virchows Arch., 1913, ccxii, 200 (bibl.).

suppurative and necrotic lesions of the ileum and colon—Streptococcus pyogenes, Staphylococcus pyogenes, Bacillus coli communis, Bacillus proteus, Bacillus pyogenes, and others. The significance of these organisms is not yet clear.[1]

Mucous Colitis (Membranous Colitis).—Under a variety of obscure conditions, probably sometimes inflammatory in character, shreds or sheets or even cylindrical casts of the interior of the gut are passed from the bowels. These consist of dense mucus often mingled with degenerated epithelium.[2] While the phenomenon may occur in connection with chronic dysentery, chronic appendicitis, constipation, or tumor of the bowel, it is seen most frequently without evident cause in persons of a neurotic temperament; and as the disease is never of itself fatal, little is known of the underlying anatomical alterations, if such regularly exist.

Chronic Colitis.—In prolonged inflammation of the colon, marked structural alterations may take place. The glandular coat may be uniformly thickened or thrown into the form of polypoid tumors, or atrophied, or destroyed by ulcers of various sizes and shapes (Fig. 496 and

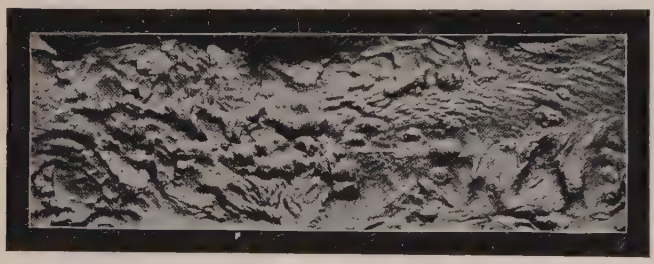


FIG. 497.—CHRONIC COLITIS WITH EXTENSIVE ULCERATION OF THE MUCOUS MEMBRANE. In places only a few ragged islets of mucous membrane are left, the muscularis forming the bottomof the ulcers.

497). Small cysts may form from the retention of mucus in the follicles. The connective-tissue and muscular coats may be thickened or thinned. Apparently chronic colitis may follow any of the forms of acute colitis.[3]

Repair may follow even considerable losses of substance in the intestinal mucous membrane. The new-formed connective tissue may un-

[1] See *Kruse* and *Pasquale*, Ztschr. f. Hyg. u. Infectionskrankh., 1894, xvi, 1; also *Cérenville*, *Tavel*, and others, Ann. Suisses des Sc. Méd., 1895, ii, 531.

See, for consideration of Streptococcus enteritidis in infants, *Hirsch*, Centralbl. f. Bakteriol., Orig., I., 1897, xxii, 369 (bibl.).

For a study of intestinal bacteria, see *van Ermengem*, Kolle and Wassermann, Handbuch. d. path. Mikroorganismen, 1st ed., 1903, ii, 637; *Ford*, Studies Royal Victoria Hospital, Montreal, 1903, vol. i,, (résumé and bibl.); *Kendall, A. I.*, Bacteriology, General, Pathological and Intestinal, Philadelphia, 1916; and Am. Jour. Med. Sc., 1918, clvi, 157; and *Cammidge, P. J.*, Feces of Children and Adults, New York, 1914. For a study of the permeability of the intestinal wall for bacteria, see *Klimenko*, Ztschr. f. Hyg. u. Infectionskrankh., 1904, xlviii, 67; and *Uffenheimer, A.*, Deutsch. med. Wchnschr., 1906, xxxii, 1851 (bibl.). See, for a study of absorption in the large intestine, *Bremer, J.*, Jour. Med. Research, 1906, N. S. x, 89. For a study of the cause of death of bacteria in the small intestine, see *Rolly* and *Liebermeister*, Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 413.

[2] For observations and bibliography of membranous enteritis or colitis consult *Butler, G. R.*, New York Med. Jour., 1895, lxii, 824 (bibl.); or *Akerland*, Arch. f. Verdauungskr., 1896, i, 396.

[3] For syphilitic types see *Gatewood* and *Kolodny*, Am. J. Syph., 1923, vii, 648.

dergo slight or marked cicatricial contraction. The denuded surfaces may become covered anew with epithelium derived from the intact cells.[1]

Anthrax Infection of the Intestine (Mycosis Intestinalis).—The anthrax bacillus may lodge in the intestinal mucosa either through food containing the germ or by metastasis through the blood from some infective focus, especially the skin.[2]

The intestinal lesions are most apt to occur in the small intestines and in the upper part of the colon. The mucous membrane is studded with larger and smaller brown or black, frequently elevated patches, or areas of local congestion, or hemorrhage, or necrosis. The mucous membrane near the inflammatory and necrotic foci may be edematous. Hyperplasia of the spleen and lymph-nodes is apt to accompany the intestinal anthrax. The anthrax bacillus may be found about the seat of local lesion in the intestine, in the associated lymph-nodes; and when secondary to local infection elsewhere it may be found in the primary lesion and in the blood.

It is believed that other forms of bacteria may cause intestinal lesions somewhat similar to those of anthrax, but the researches in this direction are not yet sufficiently numerous to permit of very definite statements.

Actinomycosis of the intestine is rare. It may give rise to tumor-like masses of inflammatory tissue, in which the fungi can be demonstrated. The portal of entry is through the mucous membrane, most often of the appendix, and there is presumably a previous slight injury of the mucosa by sharp particles of food.[2]

The Cecum.

Catarrhal Inflammation of the cecum is not uncommon. It is usually produced by an habitual accumulation of feces in this part of the intestine. The course of the inflammation is usually chronic, but marked by acute exacerbations. At first the mucous membrane undergoes the ordinary changes of chronic catarrhal inflammation. To this may succeed a slow suppurative inflammation which extends through the wall of the intestine and gives rise to ulcers and perforations.

Through these perforations the feces may pass into the peritoneal cavity, or the perforations may be partly closed by adhesions, and abscesses, or sinuses into the surrounding soft parts may be formed.

Chronic Hyperplastic Tuberculosis of the Ileocecal Region and Other Parts of the Intestine.—Attention has recently been called to a peculiar form of tuberculous inflammation of the intestine which is characterized by the extensive formation of small spheroidal-cell and fibrous tissue, especially in the submucosa and often involving the muscular wall and the subserous layer. Miliary tubercles, cheesy degeneration, and ulceration are not usually conspicuous features of the lesion. The ileocecal region is most often involved, the rectum less frequently, while the lesion is rarely limited to the ileum. Both the large and small intestines may

[1] For a study of regeneration of intestinal epithelium, see *Quénu* and *Branca*, Arch. d. méd. expér., 1902, xiv, 405. For a study of the association of the crypts of Lieberkühn with lymph-nodules in the colon, see *Schultze, W.*, Centralbl. f. allg. Path., 1905, xvi, 99.

[2] *Brumbaugh, A. S.*, Jour. Am. Med. Assn., 1919, lxxii, 482.

[3] *Harbitz* and *Gröndahl*, Zieglers Beitr., 1911, 1, 193.

be involved together. The new tissue may form a circumscribed annular thickening of the wall of the gut, or it may occur as a distinct tumor or as polypoid projections of the mucous membrane. The intestine in the vicinity of the involved portion may be inclosed in a mass of fibrous fat tissue. Owing to the thickening of the wall of the intestine the lumen may be much narrowed or nearly completely stenosed. On section of the thickened areas, caseous foci may be revealed; ulcerations, in rare cases, may be absent; more often they are moderate or extensive.

The microscopical examination shows that while miliary tubercles and cheesy degeneration are commonly to be detected, the new tissue consists in the main of collections of small spheroidal cells with more or less fibrous stroma and occasionally giant cells, and of moderately cellular or dense fibrous tissue. The polyhedral cells common in tuberculous inflammation are not as a rule conspicuous. The new tissue is usually most abundant in the submucosa. The mucosa may be similarly thickened, usually in polypoid form, or unchanged; it may show simple catarrhal alterations or may contain miliary tubercles or be ulcerated. The muscular coat also may be infiltrated and much thickened by the new-formed cellular and fibrous tissue and there may be muscular hypertrophy. The associated lymph-nodes may be involved. Tubercle bacilli are present in the lesions, sometimes in enormous numbers. The process appears to be sometimes primary in the intestine; sometimes it occurs with or follows tuberculous lesions of the lungs. Hyperplastic tuberculous lesions limited to the cecum have frequently been operated upon because the process was thought to be cancerous.[1]

The Rectum.

Besides *inflammatory changes* similar to those already described as occurring in the colon, we sometimes find a suppurative inflammation of the connective tissue which surrounds the rectum, either associated with lesions of the mucous membrane or occurring by itself.

In adults the lower end of the rectum is the part of the intestine which is the most frequent seat of syphilitic ulceration.[2] Most of these ulcers seem to be the result of unnatural coitus, or of infection from specific sores of the vulva; but some of them seem to be due to the softening of gummy tumors. The gonococcus, also, is an occasional excitant of inflammation of the rectum, and some of the lesions previously classed as syphilitic may be due to this agent.[3] Microscopically, an extensive and diffuse plasma-cell infiltration is found, with perivascular collections and swelling of the endothelium.

Strictures of the rectum may be due to tumors, to cicatrices following trauma, or to inflammation.[4]

[1] *Wiener, J.*, Ann. Surg., 1914, lix, 698; *Gage* and *Hunt*, Boston Med. and Surg. Jour., 1917, clxxvi, 259; *De Nancréde, C. B. G.*, and *Butterfield, E. E.*, Surg., Gynec., and Obst., 1906, iii, 302.

[2] *Herxheimer, G.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1906, x^1, 1; 1908, xii, 499.

[3] *Exner, A.*, Ztschr. f. Chir., 1911, cix., 261.

[4] For bibliography of non-malignant rectal strictures see *Peterson*, Jour. Am. Med. Assn., 1900, xxxiv, 259.

Hemorrhoids (Piles).—Ectasias of the hemorrhoidal veins are of frequent occurrence. They are most frequent in adults and are usually due to venous obstruction in cirrhosis, chronic constipation, pelvic tumors, chronic inflammation of the rectum, etc. The enlarged veins may be within or without the sphincter—internal or external hemorrhoids. The dilated veins may have thickened walls and may be surrounded by new-formed connective tissue. The projecting mass in external hemorrhoids may consist in part of dilated vessels, in part of fibrous tissue, and is covered by thickened epithelium (Fig. 498). Considerable hemorrhage may take place from hemorrhoids, and they may afford a portal of entry of bacteria leading to local or general infection.

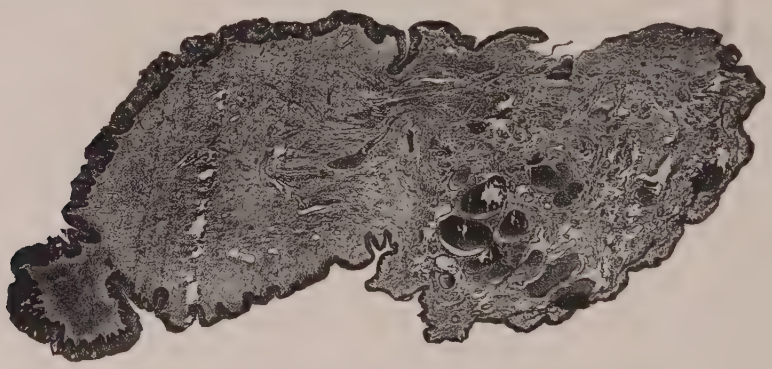


FIG. 498.—HEMORRHOID.

Section of an external hemorrhoid consisting of fibrous tissue and dilated vessels. Covered with epithelium except at the upper right portion where it was attached.

THE APPENDIX VERMIFORMIS.

Inflammation—Appendicitis.—Inflammation of the appendix may present various phases.

1. The mucous membrane may be the seat of *acute catarrhal inflammation*. This is of mild type and short duration, with congestion, swelling, and an increased production of mucus; or it is of severer type, of longer duration, and the cavity of the appendix is distended by mucus and pus.

2. The entire thickness of the wall of the appendix may be the seat of an *acute exudative inflammation*. The appendix is very much increased in size, sometimes to the size of a man's finger (Fig. 499). This increase in size is due, not to a dilatation of the cavity of the appendix, but to a thickening of its walls. The walls are congested, swollen, infiltrated with fibrin and pus, the peritoneal coat is covered with fibrin. There is neither necrosis nor perforation. If the appendix is behind the cecum, or if adhesions are formed early, there is only a localized peritonitis. If the appendix projects freely into the peritoneal cavity and no adhesions are formed, a general peritonitis may be soon established.

3. At one or more points in the wall of the appendix there is an *exudative inflammation with necrosis*. In this way small or large portions of

the wall of the appendix are destroyed, large or small perforations are formed, and the contents of the appendix escape into the abdominal cavity. In these cases the appendix often contains a fecal concretion. Such perforations are usually followed by the collection of pus around the appendix (Fig. 500). The pus may extend from this abscess-like collection in any direction and for long distances, so that collections may be found deep in the pelvic cavity, or under the diaphragm, or abscesses may form at other remote points.

Fig. 499.—Acute Appendicitis.
A posterior view of the caput coli. The appendix is swollen and a pellicle of exudate covers it and the adjacent intestine.

4. The entire appendix may become *gangrenous* within one or two days, with the formation of an abscess, or general peritonitis. This is the most usually fatal form of appendicitis.

5. Inflammation of the appendix may be *secondary* to *catarrhal* or *croupous colitis*.

6. In *typhoid fever* there may be changes in the wall of the appendix of a character similar to those in the wall of the small intestine; that is, hyperplasia of the lymphoid tissue and endothelial cells with necrosis (page 271).

7. There may be a *tuberculous inflammation* of the appendix, with the ormation of ulcers.

As the result of chronic inflammation in the appendix, atrophy of the

glands and lymphoid tissue with increase of the fibrous tissue (Fig. 501) and *strictures* or *obliteration* of its lumen may occur (Fig. 502) often corre-

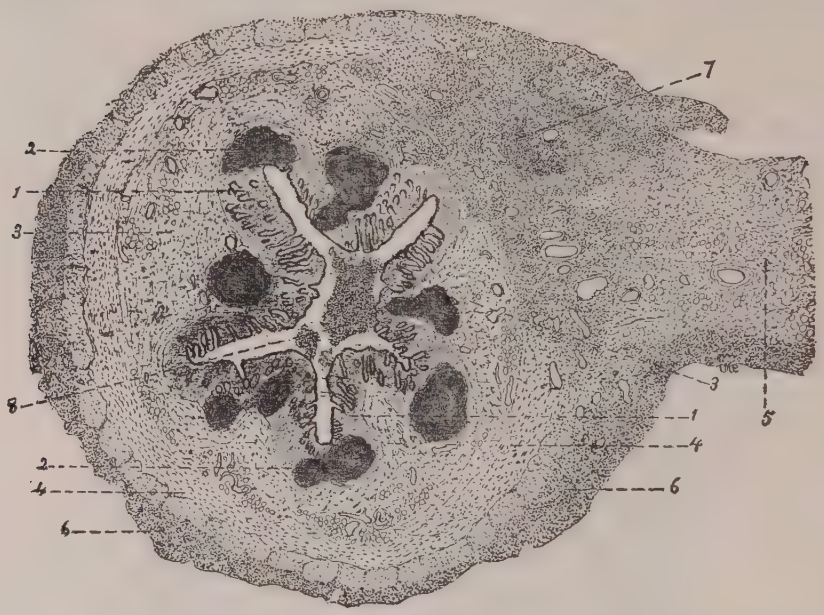


FIG. 500.—ACUTE SUPPURATIVE APPENDICITIS.

Appendix removed by operation twelve hours after first symptoms. Streptococcus was found in the exudate. 1, Mucous membrane of the appendix; 2, lymphatic nodules in the mucous membrane; 3, submucosa; 4, muscularis; 5, mesentery of the appendix; 6, pus and fibrin covering the appendix; 7, dense infiltration of the wall of the appendix with pus; 8, pus exudate in lumen.

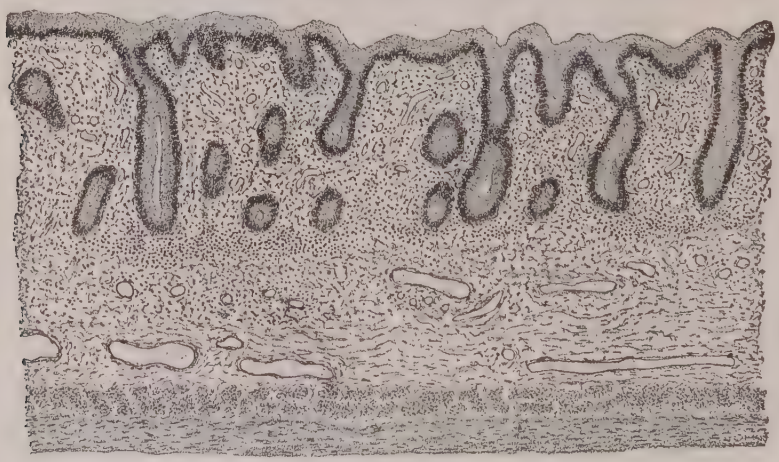


FIG. 501.—CHRONIC APPENDICITIS.

Showing obliteration of the glands and lymphoid tissue with new fibrous tissue in the mucosa and submucosa.

lated with extensive arterial changes. Such chronic inflammation does not always lead to obliteration of the appendix, but may cause only a

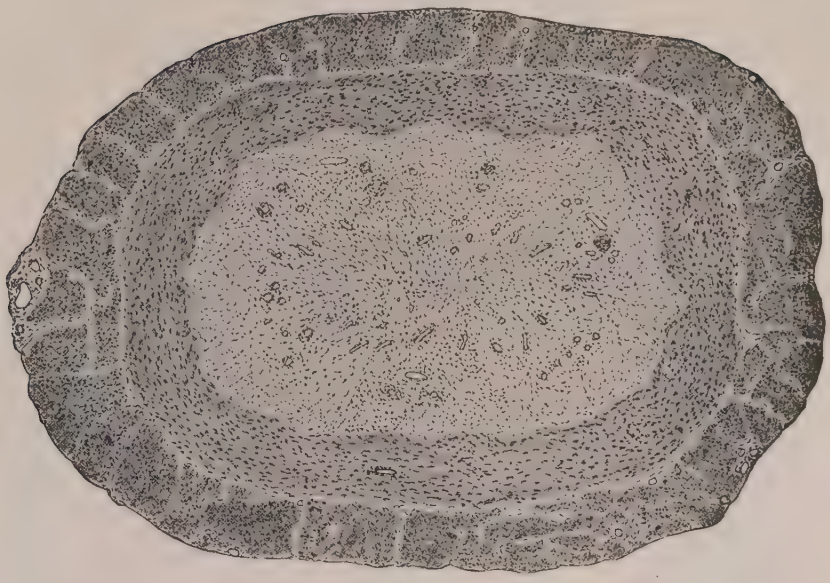


FIG. 502.—APPENDIX WITH OBLITERATION OF THE LUMEN BY FIBROUS TISSUE.

FIG. 503.—EOSINOPHILIA IN SUBMUCOSA OF APPENDIX.
No parasites were present.

thickening of the wall and extensive infiltration with eosinophiles and plasma cells (Fig. 503).[1]

Cystic dilatation of the appendix may be formed by obstruction of the lumen. The cysts thus formed may be of considerable size—from one to fifteen centimeters in diameter or larger—and contain mucous, gelatinous, or watery fluid often turbid or colored.[2]

The lumen of the appendix frequently contains *concretions* of fecal material which have been mistaken for foreign bodies. Foreign bodies,

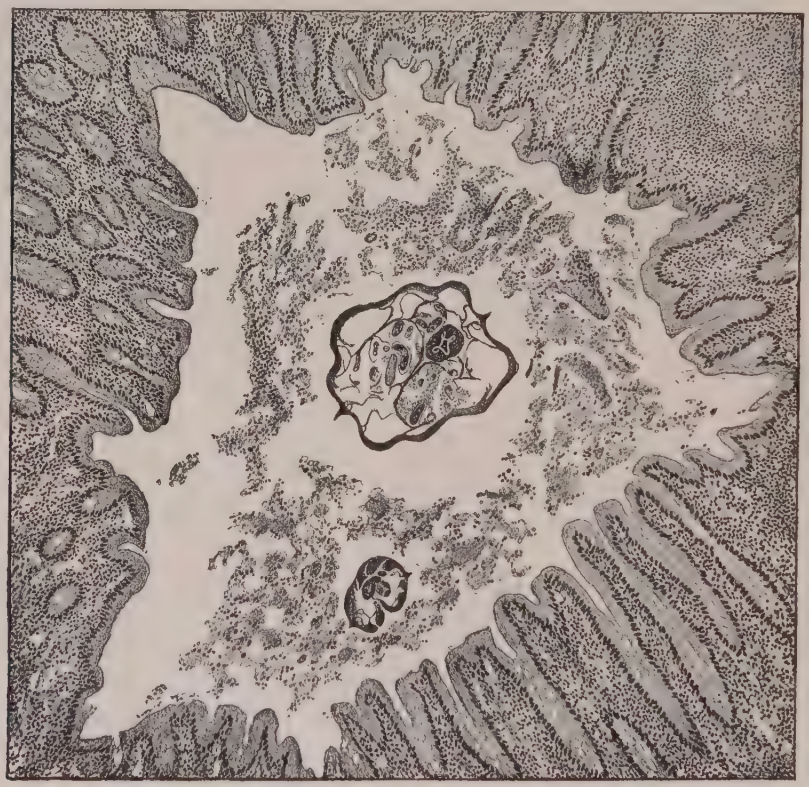


Fig. 504.—Appendix with Oxyuris Vermicularis in Cross Section.

such as grape and apple seeds, shot, pins, and various other small objects which have been swallowed, sometimes, though rarely, find their way into the appendix.[3] Both the fecal concretions and the foreign bodies may act as important predisposing agents of inflammation and perforation of the appendix, through pressure, erosion, etc., of the mucous membrane, affording portals of entry to various forms of pathogenic microorganisms.

[1] *Weir, W. H.*, Jour. Am. Med. Sc., 1903, cxxv, 74.

[2] See, for a study of cysts and diverticula of the appendix, *Corning*, Albany Med. Ann., 1905, xxvi, 816; and *Winkler*, Erkrankungen des Blinddarmanhanges, Jena, 1910.

[3] For a study of foreign bodies in appendix, see *Mitchell*, Bull. Johns Hopkins Hosp., 1899, x, 35 For report of cases in which concretions were demonstrated by Roentgen rays, see *Douglas* and *LeWald* Jour. Am. Med. Assn., 1916, lxvi, 1919.

The bacteria most commonly found associated with the lesions of acute appendicitis and its accompanying peritonitis are Streptococcus pyogenes, Staphylococcus pyogenes, the B. coli communis, B. proteus, and B. pyocyaneus. Anaerobic forms are also important.[1]

Oxyuris and trichocephalus are frequently found in the appendix in children, and may by their destruction of the mucosa permit the entry of bacteria (Fig. 504).[2]

TUMORS OF THE INTESTINE.

Primary tumors of all types, both benign[3] and malignant, are comparatively rare in the small intestine. Malignant growths are perhaps more common than benign, sarcomata being the most frequent malignant tumor found; in the large intestine, however, it is carcinoma which occurs most often.

FIG. 505.—SMALL POLYP OF THE MUCOUS MEMBRANE OF THE SMALL INTESTINE.

Fibromata[4] and **lipomata**[5] may be developed from the submucous coat and grow inward, or from the subserous coat and project outward into the peritoneal cavity.

Small multiple **cavernous hemangiomata** are of occasional occurrence in the submucosa of the small intestine, to which they may be limited; on the other hand, they may be found throughout the whole gastrointestinal tract.[6]

Myoma may originate in the muscular coat and project inward, diminishing the lumen; in the duodenum such tumors may obstruct the common bile duct. Less frequently these growths project outward into the peritoneal cavity.

Adenomyoma has been described, and referred to congenital pancreatic remnants[7] or to developmental displacements of fragments of the mucous membrane.[8]

Polypoid growths, projecting into the cavity of the intestine and composed of connective tissue covered by epithelium, are frequently found

[1] *Hodenpyl, E.*, New York Med. Jour., 1893, lviii, 777. Consult also *Kelynack*, Pathology of the Vermiform Appendix, London, 1893; *Berry, R.*, Jour. Path. and Bacteriol., 1895, iii, 160 (bibl.); *Ribbert*, Virchows Arch., 1893, cxxxii, 66. For bacterial reports, see *Low*, Reports of Boston City Hosp., 1900, Ser. 11, p. 173; *Lanz* and *Tavel*, Rev. de chir., 1904, xxx, 43; and *Perrone*, Ann. Inst. Pasteur, 1905, xix, 367. For comprehensive treatise, see *Kelly* and *Hurdon*, Diseases of the Vermiform Appendix, Philadelphia, 1905; *Aschoff*, Die Wurmfortsatzenzündung, Jena, 1908; and *v. Brunn*, Ergebnisse der Chir., 1911, ii, 32.

[2] *Cecil* and *Bulkley*, Jour. Exper. Med., 1912, xv, 225; *Aschoff*, Berl. klin. Wchnschr., 1914, l, 1504; and *Suzuki, K.*, Surg., Gynec., and Obst., 1915, xxi, 702.

[3] For an extensive discussion and bibl. of benign tumors of the intestine, see *King*, Surg., Gynec., and Obst., 1917, xxv, 54.

[4] *James* and *Sappington*, Ann. Surg., 1917, lxv, 109 (bibl.); *King*, Surg., Gynec., and Obst., 1917, xxv, 54.

[5] *Harrigan*, Boston Med. and Surg. Jour., 1917, clxxvi, 535 (bibl.); *Tromp*, München. med. Wchnschr., 1915, lxii, 1215 (bibl.); *Stetten*, Surg., Gynec., and Obst., 1909, ix, 156 (bibl.).

[6] *Bennecke*, Virchows Arch., 1906, clxxxiv, 171; *MacCallum*, Bull. Johns Hopkins Hosp., 1906, xvii, 258.

[7] *Trappe*, Frankfurt. Ztschr. f. Path., 1907, i, 109 (bibl.); *Saltykow*, Zieglers Beitr., 1912, liv, 559, (bibl.).

[8] *Meyer, R.*, Verhandl. d. deutsch. path. Gesellsch., 1908, xii, 148.

(Fig. 505).[1] They are associated with catarrhal inflammation or occur in its absence; they are found throughout the intestinal tract and may be single or multiple They are most common in the large intestine and the rectum, springing from the submucous coat and projecting inward.[2] Some are solid connective tissue tumors, while others are spongy and contain tubules lined with cylindrical epithelium giving to the growth the character of an adenoma.

Lymphoma.—Growths somewhat resembling the lymphatic tissue of the lymph-nodes may originate in the solitary and agminated nodules and in the intestinal wall in cases of leukemia and pseudoleukemia (Fig. 506). Similar growths are found as independent lesions in both the large and the small intestine; they are irregular diffuse nodules infiltrating the wall, the mesentery, and the neighboring lymph-nodules and may reach

FIG. 506.—"LYMPHOMATA" OF THE INTESTINE IN PSEUDOLEUKEMIA.
The growths are polypoid, many are pigmented, and they were in this case widely distributed over the intestinal mucosa.

a considerable size. They often ulcerate internally and sometimes lead to dilatation and stenosis.

Carcinoid Tumors.[3]—These are small nodules, a few millimeters in diameter and often multiple, which are found in middle-aged people in the submucous coat of the small intestine opposite the attachment of the mesentery. They are whitish in color, freely movable, and covered by intact mucous membrane. They grow slowly and rarely metastasize. Upon morphological examination they are found to consist of anastomosing nests and columns of closely packed cells with round nuclei and sometimes arranged after the manner of a gland. They are sharply encapsulated and exhibit no tendency to penetrate the muscular coat. Their acellular stroma may contain smooth muscle fibers. The name carcinoid has been applied to these tumors because they resemble carcinoma mor-

[1] For a general discussion of these and their relation to carcinoma, see *Versé*, Uber die Entstehung, den Bau u. das Wachstum der Polypen, Adenome u. Karzinome des Magen-Darmkanals, Arb. a. d. path. Inst. z. Leipzig, 1908, Erster Band; and *Hauser*, Das Cylinderepithel-Carcinom des Magens u. d. Dickdarms, Jena, 1910.

[2] *Carroll*, Surg., Gynec., and Obst., 1915, xx, 412 (bibl.).

[3] *Oberndorfer*, Frankfurt. Ztschr. f. Path., 1907, i, 426 (bibl.); *Saltykow*, Zieglers Beitr., 1912, liv, 559 (bibl.); *Dietrich*, Frankfurt. Ztschr. f. Path., 1913, xiii, 390 (bibl.); *Vance*, Proc. New York Path. Soc., 1916, xvi, 158 (bibl.).

phologically but not biologically. Recent studies point to their origin from the cells of crypts of Lieberkühn, which belong to the chromaffine system. These cells have an affinity for silver, hence the carcinoids may properly be called argentaffine tumors.[1] Their relationship to nerve filaments explains the acute symptoms which they sometimes cause.[2] Similar tumors occur in the appendix (page 797).

Sarcomata[3] are of occasional occurrence in the intestine, as has already been said. They are rare in the large intestine, with the exception of the rectum.[4] *Melanotic sarcoma* has been described in the small intestine[5] and in the rectum.[6]

While various types of sarcoma have been recorded, *lymphosarcoma*[7] is the most common; this sometimes gives the clinical symptoms of appendicitis.[8]

FIG. 507.—ADENOMA OF THE RECTUM.
The glands, as is not uncommon in polypoid adenomata of the intestine, are seen in the submucosa, although the tumor is benign.

Adenomata are found in the duodenum, colon, and rectum. They form superficial infiltrations of the intestinal wall or project inward as polypoid tumors. They are composed of tubular follicles like those of the mucous membrane, and of a connective tissue stroma. In some, the tubules have a regular shape and arrangement and do not infiltrate the surrounding tissue; the tumor is of benign nature. In others, however, the tubules are irregular in shape and arrangement, and the growth infiltrates the neighboring parts (Fig. 507). As with the bladder, it is

[1] *Forbus*, Johns Hopkins Hosp. Bull., 1925, xxxvii, 130 (bibl.).
[2] *Masson, P.*, Annales d'anatomie pathologique, 1924, i, 3.
[3] *Storch*, Deutsch. Ztschr. f. Chir., 1904, cxxviii, 218 (bibl.); *Douglass*, Ann. Surg., 1912, lv, 400 (bibl.); *Miller*, Surg., Gynec., and Obst., 1913, xvii, 210 (bibl.); *Libman*, Am. Jour. Med. Sc., 1900, cxx, 309.
[4] For bibl. of sarcoma of the large intestine, see *Jopson* and *White*, Am. Jour. Med. Sc., 1901, cxxii, 807.
[5] *Vander Veer* and *Kellert*, New York State Jour. Med., 1917, xvii, 335 (bibl.).
[6] *Weiner*, Zieglers Beitr., 1899, xxv, 322.
[7] *Eisenbrey*, Proc. New York Path. Soc., 1913, xiii, 116; *Schmidt*, Frankfurt. Ztschr. f. Path., 1915, xvi, 131 (bibl.)
[8] *Libman*, Proc. New York Path. Soc., 1913, xiii, 119 (discussion of Eisenbrey's paper).

sometimes difficult to decide whether polypoid tumors of the rectum are benign or malignant.

Carcinoma develops most often in the colon and the rectum.[1] Forms which have been described in the stomach occur here also; *i.e.*, 1, The variety with relatively little stroma and epithelial cells arranged in solid masses (*medullary type*) or maintaining in a measure the glandular arrangement (*adenocarcinoma* Fig. 508 and 509). 2. *Scirrhus.* 3. The *gelatinous type,* which is more common here than in the stomach. 4. *Epithelioma,* which often involves the rectum and anus.

FIG. 508.—ADENOCARCINOMA OF THE RECTUM.
Shows a portion of normal mucous membrane invaded by the new growth. This type of tumor is frequently, but improperly, called malignant adenoma.

Cysts of the intestine are uncommon.[2] One type (*gas cyst*) appears as multiple cavities containing gas and scattered through the intestinal wall.[3]

Dermoid cysts are most frequently observed in the small intestine, where they may be subserous, intramuscular, or submucous.[4]

TUMORS OF THE APPENDIX.[5]

Tumors of the appendix are not frequent; **fibroma, lipoma, myoma,** and **sarcoma**[6] have been found.[7]

[1] *Rolleston,* Lancet, 1901, i, 1121. For a general discussion of various types of intestinal carcinoma, see *Hauser,* Das Cylinderepithel-Carcinom d. Magens u. d. Dickdarms, Jena, 1910.

[2] *Ayer,* Am. Jour. Med. Sc., 1906, cxxxi, 89.

[3] *Thalhimer,* Proc. New York Path. Soc., 1913, xiii, 5 (bibl.); *Schnyder,* Cor.-Bl. f. schweiz. Aerzte, 1917, xlvii, 289.

[4] *Jepson,* Surg., Gynec., and Obst., 1905, i, 319.

[5] For a general discussion of tumors and other diseases of the appendix, see *Oberndorfer,* Lubarsch-Ostertag, Ergebn. d. allg. Path., 1909, xiii[1], 527 (bibl.); *Winkler,* Die Erkrankungen des Blinddarmanhanges, Jena, 1910.

[6] *Jones,* Surg., Gynec., and Obst., 1911, xii, 131 (bibl.).

[7] For bibl. of tumors of the appendix, see *Kelly,* Proc. Path. Soc., Philadelphia, 1900, N. S. iii, 109; *Miloslavich* and *Namba,* Ztschr. f. Krebsforsch., 1913, xii. 14; *Crouse,* Surg., Gynec., and Obst., 1910, xi, 457.

Carcinoid Tumors.[1]—There is sometimes found in the appendix a peculiar and characteristic growth, the nature of which is as yet undetermined (Fig 510). It usually involves the muscularis or submucosa and is discovered in about 0.5 per cent. of all appendices removed,[2] particularly in younger patients. It consists of alveoli filled with rather large clear cells of uniform size, packed closely together and bearing vesicular nuclei with prominent nucleoli; mitotic figures are not often found. The condition is rarely diagnosed during life, but is discovered accident-

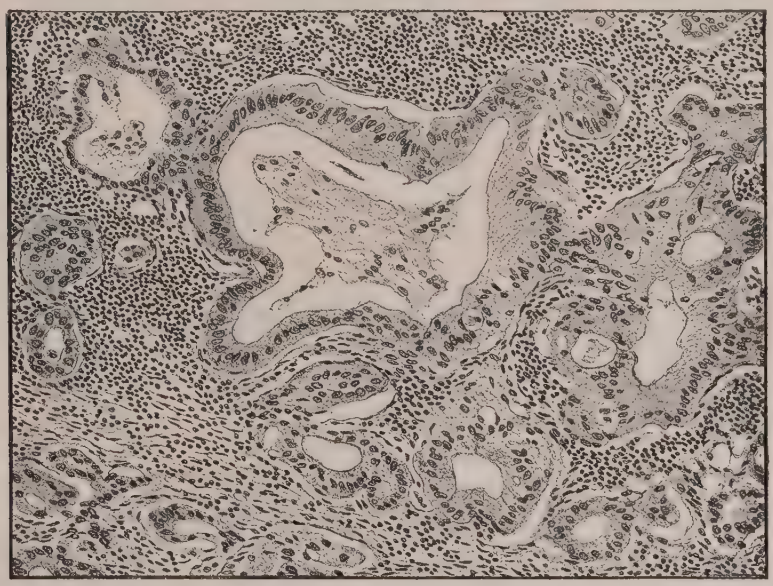


Fig. 509.—Glandular Carcinoma of Intestine.

ally in appendices extirpated for other reasons. By some observers the growth is regarded as a *carcinoma*, though only an occasional one proves to be malignant.[3] Other writers prefer some such term as *pseudocarcinoma, carcinoid tumor*[4] (on account of its morphological resemblance to *carcinoid tumors* of the intestine (see page 794), or *nævus*.[5]

Cylindrical-cell cancer, sometimes forming much mucoid material and of a morphological type similar to that found in any other part of the gastrointestinal tract, may develop in the appendix,[6] though it is extremely rare (Fig. 511).

[1] *Rolleston* and *James*, Am. Jour. Med. Sc., 1906, cxxxi, 951 (bibl.); *Whipham*, Lancet, 1901, i, 319; *Jessup*, Med. Rec., 1902, lxii, 289; *Moschcowitz*, Ann. Surg., 1903, xxxvii, 89 (bibl.); *Norris*, Univ. Pennsylvania Med. Bull., 1903, xvi, 334; *McWilliams*, Am. Jour. Med. Sci., 1908, cxxxv, 822; *Gerlach, P.*, Frankfurter Ztschr. f. Path., 1920, xxiv, 515 (bibl.); *Vance*, Proc. New York Path. Soc., 1916, xvi, 158 (bibl.).

[2] *Meyer*, Surg., Gyn., and Obst., 1915, xxi, 354 (bibl.); *Rogg*, Ztschr. f. Krebsforsch., 1913, xii, 12 (bibl.); *Mayo, C. H.*, Jour. Am. Med. Assn., 1910, lv, 1605.

[3] *Luce*, Beitr. z. klin. Chir. (Bruns), 1912–13, lxxxii, 155 (bibl.).

[4] *Oberndorfer*, Frankfurt. Ztschr. f. Path., 1907, i, 426 (bibl.).

[5] *Aschoff*, Pathologische Anatomie, 3d ed., Jena, 1913, p. 831.

[6] *Miloslavich*, Frankfurt. Ztschr. f. Path., 1913, xiii, 138; *Miloslavich* and *Namba*, Ztschr. f. Krebsforsch., 1913, xii, 14 (bibl.).

Cysts.[1]—A rather uncommon condition (*pseudomucinous cyst, hydrops spurius*) is the result of obliteration of the lumen of the appendix near

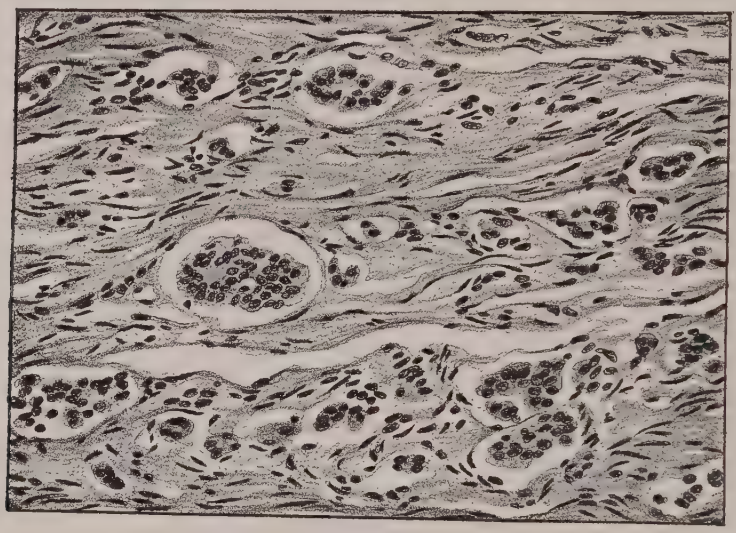


FIG. 510.—CARCINOMA OF APPENDIX.
Carcinoid type.

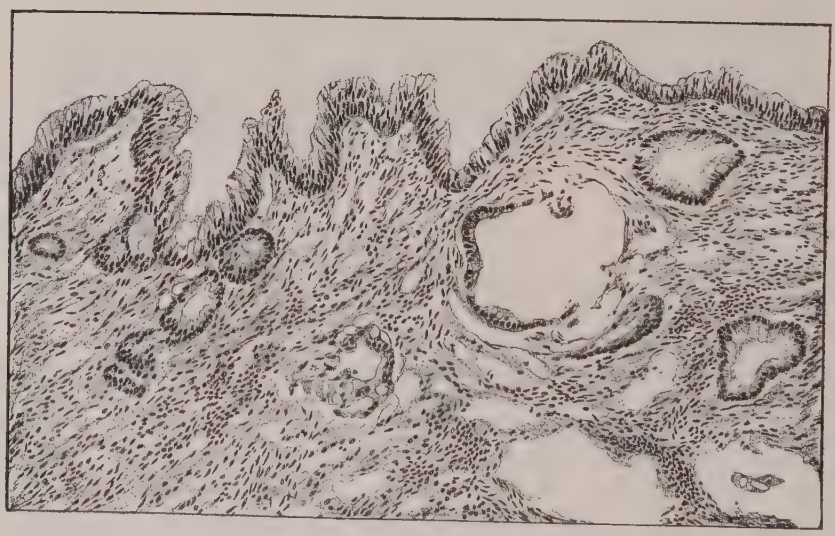


FIG. 511.—GELATINOUS CARCINOMA OF APPENDIX.

its proximal end and dilatation of the remainder; the wall of the resulting cyst may undergo calcification.[2] Sometimes the wall ruptures and par-

[1] For bibliography see *Crouse*, Surg., Gynec., and Obst., 1910, xi, 457.
[2] *Ogilvie*, Jour. Am. Med. Assn., 1915, lxiv, 657 (bibl.).

ticles of the mucous membrane escape into the peritoneal cavity, where they have the power to grow[1] (see page 808).

INTESTINAL CONCRETIONS. (Enteroliths.)

The intestines may contain round, oval, or irregular masses of firm consistence, usually small, but sometimes as large as a man's fist. They consist of fecal matter, mucus, bile, the carbonate and phosphate of lime, and triple phosphate. They may induce inflammations, ulceration, and perforation. Small brown concretions—*intestinal sand*—may be found. A large part of such bodies are derived from the ligneous "stone cells" contained in some fruits, upon which calcium salts collect.

PIGMENTATION OF THE INTESTINE.

A moderate amount of pigmentation is frequently noted in the large intestine after bleeding from any portion of the gut, after severe inflam-

FIG. 512.—PIGMENTED INTESTINE.

matory lesions, and, also, following chronic intoxication with silver, mercury, and bismuth. The Peyer's patches may be blackened by absorption of coal-dust or soot.[2] There is, in addition, a somewhat rare form of melanosis of the large intestine which is limited to that portion of the gut. The color of the mucous membrane varies from dark brown to pure black; and the pigment is, as a rule, confined to the mucous membrane, the remainder of the wall being free, while the lymph-nodes of the mesocolon and all the other organs of the body, also, are free from any abnormal pigmentation. Very infrequently the pigment-bearing cells may be found in the submucosa or the mesenteric nodes. The pigment itself is

[1] *Oberndorfer*, Verhandl. d. deutsch. path. Gesellsch., 1906, x, 235.
[2] *Lubarsch*, Deutsch. med. Wcshnchr., 1915, xli, 1025.

amorphous, and composed of minute granular masses, and lies within large mononuclear pigment cells (Fig. 512), though occasionally it is set free in the tissues on the death of the cells of this type. It gives no iron reaction and is not affected by concentrated acid. It is probably due to the local formation of melanin from some of the decomposition products of the proteins during their absorption through the intestinal wall.[1]

The Peritoneum.

Malformations.

Arrest in development of the peritoneum may be manifested in fissures in the mesial line or external to it; in partial[2] or complete absence of the diaphragm; in fusion with the pleura; and in incomplete formation of the mesentery, the omentum, or the other folds of the peritoneum.

Excess of development occurs in the shape of unusual length of the mesentery, the omentum, or the other folds of the peritoneum; or of supernumerary folds and pouches. These are chiefly found in the hypogastric, iliac, and inguinal regions and near the fundus of the bladder. There may be access to these sacs by a well-defined fissure or ring, which is frequently surrounded by a tendinous band lying in the duplicature. These may give rise to internal incarceration of the intestines.

The left half of the diaphragm may have an abnormally high position with upward displacement of the abdominal viscera, particularly the stomach, on the left side, and displacement of the heart to the right. This has been called eventration of the diaphragm. It may be mistaken in diagnosis for diaphragmatic hernia.[3]

HEMORRHAGE.

Large hemorrhage into the peritoneal cavity may result from injuries to the abdominal viscera, ruptured aneurysm, etc. Punctate hemorrhages may accompany various acute infections and toxemias. Hemorrhage may occur in acute localized or general peritonitis, in obstruction of the portal circulation, in thrombosis and in embolism of the mesenteric vessels.

ASCITES.

The collection of transudate in the peritoneal cavity may accompany chronic venous congestion, especially with obstruction of the portal circulation in cirrhosis from thrombi, emboli, etc., or with chronic heart and kidney diseases. It often accompanies similar conditions in the pleura and pericardium. It may accompany chronic peritonitis.

Chylous ascites may result from a rupture of the thoracic duct or from a transudation from the chyle vessels.[4]

Chyliform Ascites.—Most frequently in abdominal carcinoma and tuberculosis, but also in other forms of chronic peritonitis with serous exudate, the peritoneal cavity may contain fluid, milky from cell detritus

[1] *Pick*, Berl. klin. Wchnschr., 1911, xlviii, 840, 884; *McFarland*, Jour. Am. Med. Assn., 1917, lxix, 1946; *Bland-Sutton*, Brit. Med. Jour., 1914, ii, 656. *Henschen, F.*, and *Bergstrand, H.*, Studien über die Melanose der Darmschleimhaut, Ziegler's Beitr., 1913, lvi, 103.

[2] *Vogel, K. M.*, Am. Jour. Med. Sc., 1913, cxlv, 206.

[3] See *Sailer* and *Rhein*, Am. Jour. Med. Sc., 1905, cxxix, 688.

[4] *Shaw*, Jour. Path. and Bacteriol., 1900, vi, 339.

and fat derived from the disintegration of degenerated mesothelial and other cells. This condition is called *chyliform ascites.*

INFLAMMATION. (Peritonitis.)

Acute Peritonitis.—Acute inflammation of the peritoneum may occur as a primary process, but is much more often secondary. In the latter case it may be associated with wounds and contusions of the wall of the abdomen; wounds, ulcers, new growths, incarcerations, intussusceptions,

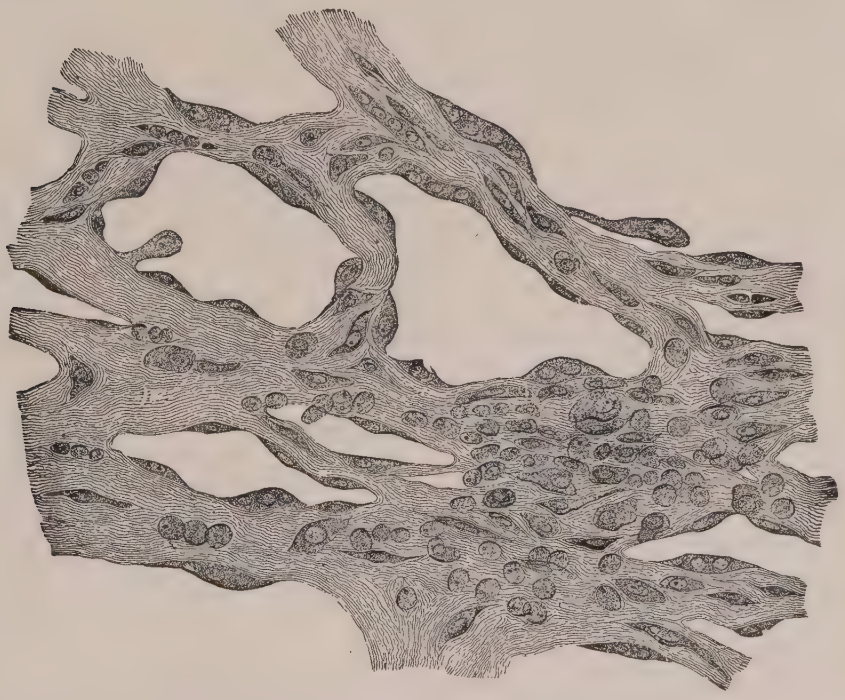


FIG. 513.—ACUTE CELLULAR PERITONITIS—HUMAN OMENTUM.
There are swelling and proliferation of the mesothelial cells as well as of the cells of the fibrillar tissue forming the omental trabeculæ.

ruptures, perforations, and inflammations of the stomach and intestines; inflammation of the vermiform appendix; injuries, ruptures, and inflammations of the uterus, ovaries, and Fallopian tubes; rupture and inflammation of the bladder; inflammation of and about the kidneys; abscesses and hydatid cysts of the liver; inflammation of the gall-bladder and large bile ducts; thrombosis of the portal vein; inflammations of the spleen, pancreas, lymph-nodes, retroperitoneal connective tissue, vertebræ, ribs, and pelvic bones; pyemia and other infectious diseases. The inflammation is at first either local or general. A local peritonitis may remain circumscribed, or it may spread and become general.

We may distinguish two anatomical forms of acute peritonitis.

1. Cellular Peritonitis.—This form of peritonitis may be induced by any irritant which does not act too energetically. It can be excited in dogs by intraperitoneal injections of very small quantities of a solution of chloride of zinc. In the human subject we find it with perityphlitis, with circumscribed abscesses in the peritoneal cavity, in puerperal fever, and in other infectious diseases with early death.

At the autopsy the entire peritoneum may be congested; but there are no exudates and no other lesions visible to the naked eye. Minute examination, however, shows a very marked change in the mesothelial (endothelial) cells. These are increased in size and number and the new cells coat the surface of the peritoneum and project outward in little masses (Fig. 513). This form of inflammation, in many cases, at least if life be prolonged, passes into the exudative phase, next to be considered.

2. Exudative Peritonitis.—This, which is the common form of acute peritonitis, presents lesions similar to those which have been already described in pleuritis and pericarditis. Thus there is a form in which fibrin is the chief exudate with but little serum; or the exudate is serofibrinous, or purulent, or hemorrhagic.[1] When fibrin is present, the intestinal coils may be more or less firmly adherent to the abdominal walls or to each other. If putrefactive bacteria are present, as in peritonitis from perforation of the intestine, the exudate may be foul.

In local inflammation of the peritoneum the position may be indicated by the name, thus perihepatitis, perisplenitis, perityphlitis, pelvic, subphrenic, etc.

Acute exudative peritonitis may terminate in recovery with absorption of the exudate, permanent connective-tissue adhesions and thickenings of the peritoneum often remaining. Chronic peritonitis may follow the acute phase.

Bacteria are the usual excitants of acute exudative peritonitis. In primary forms of peritonitis the Streptococcus and Staphylococcus pyogenes are the bacteria most frequently present.

In secondary exudative peritonitis the pyogenic cocci and the colon bacillus have been most frequently found. Of the other bacteria which have been found in the exudate we may name the pneumococcus,[2] the gonococcus,[3] B. pyocyaneus, B. proteus, B. aërogenes capsulatus, B. typhosus.

There is abundant evidence that bacteria can pass from the intestinal cavity through its wall into the peritoneum without perforation, especially in regions where the integrity of the tissues is impaired by disturbances in circulation and nutrition, or in necrosis, as in strangulation of the gut.[4]

[1] For a study of the forms of cells in exudative peritonitis, see *Lossen*, Deutsch. Arch. f. klin. Med., 1906, xxxvi, 217.

[2] *Rischbieth, H.*, Quart. Jour. Med., 1911, iv, 205.

[3] See *Cushing* on gonococcus peritonitis, Bull. Johns Hopkins Hosp., 1899, x, 75..

[4] Consult, for studies and bibliography of various phases of peritonitis, *Tavel* and *Lanz*, Peritonitis, Mitt. a. d. kl. u. med. Inst. d. Schweiz, I Reihe, 1893, i, 1; *Silberschmidt*, ibid., 1894, v, 342; *Flexner, S.*, Philadelphia Med. Jour., 1898, ii, 1019; *Cullen, T. S.*, Johns Hopkins Hosp. Rep., 1895, iv, 411; *Abramow*, Zieglers Beitr., 1898, xxiii, 1; *Büttner*, ibid., 1899, xxv, 453.

For special studies on the entrance of microorganisms into the body from the gastrointestinal canal, see *Opitz*, Ztschr. f. Hyg., 1898, xxix, 505; *Birch-Hirschfeld*, Zieglers Beitr., 1898, xxiv, 304; *Buchbinder*,

Absorption from the Peritoneum.—In connection with inflammation, recent studies which have been made of the absorption of alien substances injected into the peritoneal cavities of animals, especially rabbits and guinea-pigs, are of extreme interest and importance. Living bacteria as well as various kinds of inert particles may be rapidly disposed of through the action of the body fluids or phagocytic cells. The studies of Buxton and Torrey[1] indicate that after an intraperitoneal injection of suspensions of inert particles there may be an immediate rush of these to the lymphatics of the diaphragm, whence they are carried almost immediately by the anterior mediastinal lymph-trunks through the lymph-nodes to the thoracic duct and general circulation. In the earlier stages the transported particles may be free, but later may be taken up by phagocytes in the mediastinal lymph-nodes. But the omentum appears to be of significance in the disposal of inert particles injected into the peritoneal cavity. Buxton and Torrey showed that almost immediately after the injection of such particles in the guinea-pig, fibrin is formed on the surface of the omentum in which the particles and phagocytic cells become entangled. The phagocytes taking up the particles may then enter the tissues. These observers have furthermore shown that after intraperitoneal injections of typhoid bacilli in the rabbit, the bacilli may become fixed upon the surface of the omentum where they may be destroyed.[2]

Chronic Peritonitis may follow the acute exudative form or may occur independently. The lesions vary. In one group of cases the peritoneum is beset with minute translucent nodules, sometimes visible, sometimes invisible to the naked eye. These are apparently formed by a local proliferation of the mesothelial and connective-tissue cells. Associated with this there may be a general irregular proliferation of the peritoneal mesothelium. This has been called *chronic cellular peritonitis.*

In other cases there are local or general fibrous adhesions, sometimes firm, sometimes loose, between the intestinal coils or between the intestine and the abdominal wall or the viscera (Fig. 514). In this way sacculated collections of serofibrinous or purulent exudate may form in the abdominal cavity. Finally chronic peritonitis may result in a dense fibrous thickening of the peritoneum, either local or widespread.

In some cases the parietal peritoneum is principally involved, in others the peritoneum of the stomach, intestines, liver, and spleen. The thickening of the capsule of the liver may be attended with a diminution in the size of that viscus. There may or may not be adhesions; serous or other exudate may be present. Great distortion of the omentum, mesentery, and other abdominal viscera may occur.

When the condition is very marked the peritoneal covering of the abdominal organs may form a thick white translucent coating, resembling the icing of a cake; hence, the term *"iced liver"* sometimes employed. Another name is *polyserositis fibrosa.* This coating can be peeled off the organ, leaving a more or less normal peritoneum. There is usually extreme ascites with a palpable spleen, so that clinically the resemblance to hepatic cirrhosis is quite striking. In some instances the pericardium and pleura, also, are involved.

Deutsch. Ztschr. f. Chir., 1900, lv, 458; *Marcus*, Ztschr. f. Heilk., 1899, xx, 427; also Wien. klin. Wchnschr., 1901, xiv, 11; *Ravenel, M. P.*, Jour. Med. Research, 1903, N. S. v, 460; and *Calmette*, Med. Record, 1908, lxxiv, 741.

[1] *Buxton* and *Torrey*, Jour. Med. Research, 1906, N. S. x, 5.

[2] For a study of the local accumulation of eosinophile leucocytes after intraperitoneal injections of bacteria, see *Opie*, Tr. Assn. Amer. Phys., 1904, xix, 136.

The course of the disease is progressive, and death results from ileus, cardiac or renal disease (which often occurs with polyserositis), or a terminal infection. The etiological factor is supposed to be of toxic or bacterial origin, but there is as yet no positive evidence in this regard.[1]

Tuberculous Peritonitis may occur in acute general miliary tuberculosis or it may be secondary to tuberculous inflammation elsewhere, as in the lungs or genitourinary organs or intestines; or it may be an independent process. The process may be local or general in the peritoneum. The lesions may be miliary in character (Fig. 515) or there may be large foci of the new-formed tubercle tissues with considerable necrosis. There may be more or less serous or serofibrinous or purulent or hemorrhagic

FIG. 514.—OLD PERITONEAL ADHESIONS BETWEEN THE UNDER SURFACE OF THE LIVER AND THE INTESTINE.

L is the liver turned over to expose the inferior surface. Many delicate fibrous cords and bands pass from the liver to the intestine, *I*. The gall-bladder, *G. B.*, is distended.

exudate. Fibrous adhesions may form between the intestinal coils and the peritoneal walls with the encapsulation of exudate. Ulceration of the tubercle tissue may occur, or it may become dense and fibrous and is then often pigmented. The tuberculous inflammation may be limited to the vicinity of tuberculous ulcers of the intestine. It may involve the omentum, which is converted into a hard, thick, dense mass at the upper part of the abdominal cavity.[2]

[1] For review and bibl. see *Kelly, A. O. J.*, Am. Jour. Med. Sc., 1903, cxxv, 116; and *Evans, G. H.*, bid., 1918, clv, 553.

[2] For bibl. with reference to operative treatment, see *Bottomley*, Reports of Boston City Hosp., 1900, Series 11, p. 118. For a full critical summary of the literature of peritonitis from 1885 to 1900, see *Brunn, M.*, Centralbl. f. allg. Path., 1901, xii, 65. For review of tuberculous peritonitis, see *Beitzke, H.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1910, xiv, 169; and *Mayo, W. J.*, Jour. Am. Med. Assn., 1918, lxxi, 6.

TUMORS.

Many of the growths loosely referred to as peritoneal tumors actually arise in the subperitoneal tissue. Among these the commonest is the lipoma, and the least common, the fibroma.

Lipoma.[1]—This arises most often in the mesentery and frequently undergoes fibrous or calcareous change. The pedicle may atrophy, leaving the tumor free in the peritoneal cavity. When lipomata grow beneath the parietal peritoneum they may form fat herniæ; thus, at the umbilicus, in the inguinal canal, along the vas deferens, in the crural ring, and in the obturator foramen, they may project outward under the skin and by

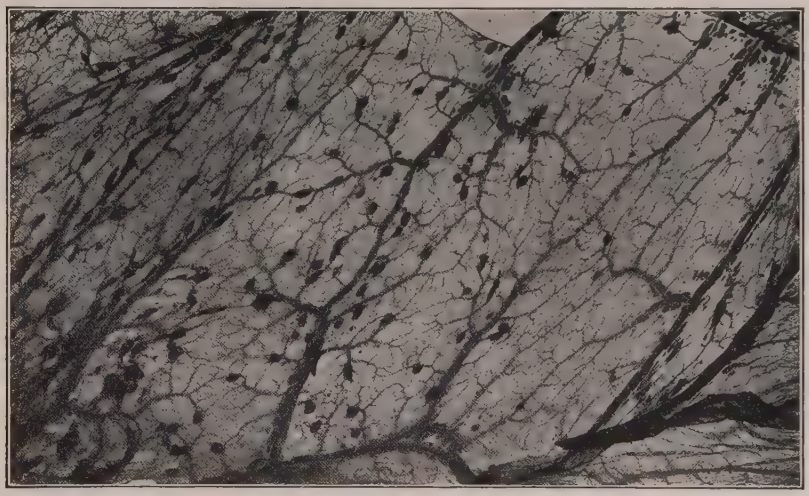


FIG. 515.—MILIARY TUBERCLES OF THE OMENTUM.

drawing the peritoneum after them open the way for a future intestinal hernia.

Very large perirenal lipomata are of occasional occurrence.[2]

Myxoma, chondroma, osteoma, and **angioma**[3] have been described.

Fibroma.—Fibromata[4] originating in the subperitoneal connective tissue may be found beneath either the parietal or the visceral peritoneum.

Retroperitoneal sarcomata[5] are found in both children and adults, sometimes extending between the folds of the mesentery.[6] Some of those

[1] *Voeckler*, Deutsch. Ztschr. f. Chir., 1909, xcviii, 149 (bibl.).

[2] *Adami*, Montreal Med. Jour., 1896–97, xxv, 529 (bibl.).

[3] For a discussion of angioma of the mesentery, see *Takano* and *Hanser*, Zieglers Beitr., 1912, liii, 105 (bibl.).

[4] *Sympson*, Lancet, 1916, ii, 188.

[5] *Steele*, Am. Jour. Med. Sc., 1900, cxix, 311. For a study of sarcoma and mixed tumors of the great omentum, see *Conforti*, Centralbl. f. allg. Path., 1906, xvii, 817.

[6] For a discussion of tumors of the mesentery, see *Bowers*, Ann. Surg., 1906, xliv, 892 (bibl.). For sarcoma of the omentum, see *Cobb*, ibid., 16 (bibl.); *Nash*, Lancet, 1911, i, 117 (angiosarcoma); *McLean*, Surg., Gynec., and Obst., 1911, xii, 588 (myxoma). For a review of primary malignant tumors of the omentum, see *Litchkous*, Ann. de gynéc. et d'obst., 1909, lxvi, 338 (bibl.) (abstr. in Surg., Gynec., and Obst., 1910, x, 218). For a study of retroperitoneal lymph-nodes and retrograde metastases of bacteria, dust, and tumor cells from the thorax into the abdomen, see *Tendeloo*, München. med. Wchnschr., 1904, li, 1537.

reported in the past may have been ganglioneuromata.[1] They may be of the small round-cell or spindle-cell type, and are often very vascular. They metastasize in the omentum, mesentery, intestinal wall, liver, lungs, and other viscera. The *fibrosarcoma* is relatively benign in this situation.[2]

FIG. 516.—CYSTIC PAPILLOMA OF THE OMENTUM.
Secondary to papilloma of the ovaries.

Tumors of the peritoneum itself are rare. They include the **mesothelioma,**[3] which is similar in all respects to that found in the pleura (page 739). Many of the so-called primary peritoneal tumors are meta-

[1] *Dunn*, Jour. Path. and Bacteriol., 1914–15, xix, 456 (bibl.); *Bland-Sutton*, Lancet, 1918, i, 429.
[2] *Bland-Sutton*, Lancet, 1918, i, 429.
[3] *Miller* and *Wynn*, Jour. Path. and Bacteriol., 1908, xii, 267 (bibl.); *Herzog*. Zieglers Beitr., **1914**, lviii, 390 (bibl.).

stases from small carcinomata overlooked at autopsy, though it is said that **endotheliomata** may arise from the lymph-vessels.[1]

Cysts of the mesentery or omentum are not particularly uncommon.[2] Various types are found—*blood cysts*, *chyle cysts*,[3] *serous cysts*, *dermoid cysts*,[4] *echinococcus cysts*, *gas cysts*, etc. Multiple cysts of the omentum may result by the transplantation of papillary cystadenomata from the ovary (Fig. 516).

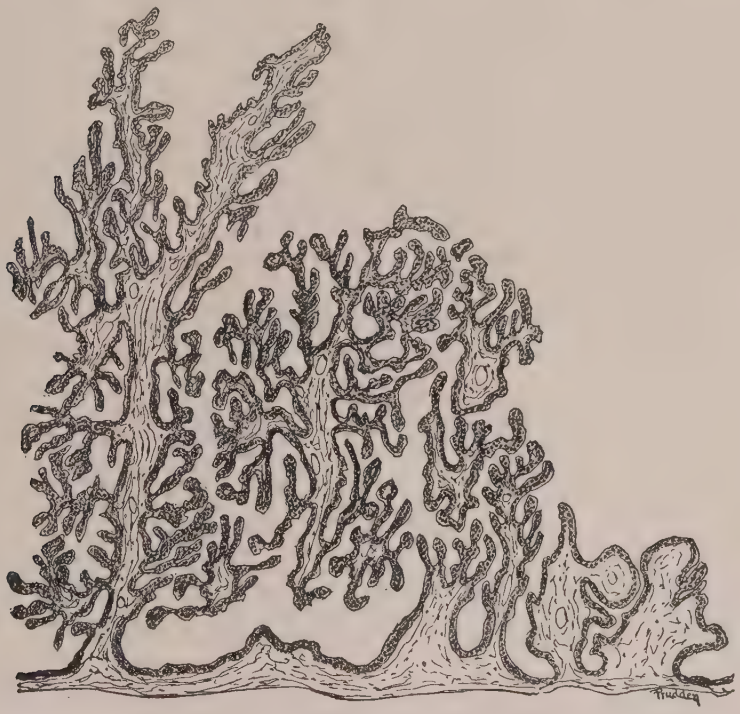


FIG. 517.—PAPILLOMA OF PERITONEUM.

This growth was secondary to a similar tumor originating in the ovary and connected with that organ (see Fig. 646). Detached portions of the original tumor were transplanted to various regions of the peritoneum.

Secondary tumors of the peritoneum include the papillary cystadenoma (Fig. 517) which is metastatic from the ovary (Fig. 646, page 978). It often involves the peritoneum, and although technically a benign tumor not infrequently causes death from the widespread involvement.

Secondary carcinoma[5] of the peritoneum is sometimes a complication of this disease in adjacent regions such as the stomach, liver, uterus, etc., and its structural characters, therefore, correspond with those of the

[1] *e.g.*, *Kaufmann*, Lehrbuch d. spez. Path., Berlin, 1911, ii, 560.

[2] *Kayser*, Beitr. z. klin. Chir. (Bruns), 1914, xciv, 52 (bibl.); *Jones*, Surg., Gynec., and Obst., 1915; xxi, 56 (bibl.); *Funk*, ibid., 1914, xviii, 70 (bibl.); *Frazier*, Jour. Am. Med. Assn., 1913, lxi, 97 (bibl.), *Dowd*, Ann. Surg., 1911, liv, 617 (bibl.).

[3] *Benedict*, Surg., Gynec., and Obst., 1913, xvi, 606 (bibl.); *Friend*, ibid., 1912, xv, 1 (bibl.); *Hadley*, ibid., 1916, xxii, 174.

[4] *Jepson*, Surg., Gynec., and Obst., 1905, i, 319 (bibl.).

[5] *Misumi*, Virchows Arch., 1909, cxcvi, 371.

primary growth. It is apt to appear in the form of whitish nodules, sometimes local, sometimes widely disseminated over the peritoneal surfaces. Such tumors, when small and numerous, may readily be mistaken for tubercles.

Pseudomyxoma Peritonei.—This obscure disease, in which the peritoneum is thickened and covered with a gelatinoid material, is also called *morbus gelatinosus* or *colloid, mucoid, muciparous, gelatinous,* or *gelatinoid carcinoma.* It is often accompanied by ascites, attacks the entire peritoneum and the underlying musculature, and appears to be in many cases a secondary carcinosis in which the invading cells suffer edematous disintegration.[1] The primary carcinoma may be in the stomach, gall-bladder, appendix or ovary.[2] In the case of the organs last named, however, the source may not be a carcinoma at all, but a mucocele, a benign cystadenoma with gelatinous contents, or a teratoma.[3] Whether in such an event the condition in the peritoneum is simply a foreign-body reaction to the gelatinous material,[4] or whether it consists of actual metastasis, is still an unsettled question.[5] It may be that two distinct processes have been included under one name. In the appendix, also, a benign process (*pseudomyxomatous cyst, hydrops spurius,* page 799) sometimes leads to pseudomyxoma of the peritoneum[6] or even of the retroperitoneal tissues.[7]

Various forms of tumors of the umbilicus have been described,[8] and some half dozen of the umbilical cord itself,[9] such as **myxosarcoma, angioma,** and **hematoma.**[10]

PARASITES.

Echinococcus cysts may be formed in their regular way at any part of the visceral and parietal peritoneum, or be free in the peritoneal cavity. These cysts may be small, or so large as nearly to fill the abdominal cavity.

Cysticercus cellulosæ may also be developed in the subperitoneal connective tissue.

The Salivary Glands—The Parotid, Submaxillary, and Sublingual.

INFLAMMATION.

Acute Parotitis, occurring as an epidemic disease known as *mumps,* is usually confined to the parotid gland of one side; the submaxillary and sublingual may be at the same time involved. The gland is swollen and

[1] *McCrae* and *Coplin,* Am. Jour. Med. Sc., 1916, cli, 475 (bibl.).
[2] *Lewis,* Surg., Gynec., and Obst., 1914, xix, 757 (bibl.).
[3] *Roth,* Zieglers Beitr., 1916, lxi, 42 (bibl.).
[4] *Werth,* Arch. f. Gynäk., 1884, xxiv, 100; *Marchand,* München med. Wchnschr., 1907, xxxiv, 1704.
[5] *Fraenkel,* München. med. Wchnschr., 1901, xlviii, 965 (bibl.).
[6] *Fraenkel,* München. med. Wchnschr., 1901, xlviii, 965 (bibl.); *Tomita,* Centralbl. f. allg. Path., 1907, xviii, 849 (bibl.); *Merkel,* Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix², 328 (bibl.); *Hueter,* Zieglers Beitr., 1907, xli, 517 (bibl.); *Bailey,* Surg., Gynec., and Obst., 1916, xxiii, 219 (bibl.).
[7] *Sturm,* Frankfurt. Ztschr. f. Path., 1915, xvi, 464.
[8] *Cullen,* The Umbilicus and its Diseases, Philadelphia, 1913, p. 351 ff.
[9] *Herweg,* Arch. f. Gynäk., 1909, lxxxix, 317 (bibl.).
[10] *Cooper,* Practitioner, 1917, xcviii, 389; *Ritter,* Centralbl. f. Gynäk., 1912, xxxvi, 641 (bibl.).

there is often edema of the mucous membrane of the mouth and pharynx. Very little is known of the minute changes which the gland undergoes in this disease.[1]

Suppurative Parotitis may occur as a secondary lesion in many diseases, typhoid and scarlet fever, pyemia, pneumonia, etc., and by bacterial invasion or extension of inflammation from the mouth. Under these conditions the process is usually suppurative and frequently results in abscess or sloughing. The interstitial tissue of the gland is more or less densely infiltrated with pus cells, and the parenchyma cells may undergo fatty degeneration and disintegration. The inflammation may be confined to the gland or it may spread to adjacent parts, sometimes causing much destruction of tissue, and may give rise to inflammation of the brain or of the inner ear, or even to metastatic pyemic abscesses in different parts of the body. Healing may occur, with formation of salivary fistulæ.

The **submaxillary gland** may be involved with the parotid in the suppurative inflammation. Acute suppurative inflammation of the connective tissue about the submaxillary gland is sometimes of serious import. Sloughing and gangrene may occur and are apt to spread to adjacent parts. Septicemia, edema of the glottis, or pneumonia may complicate the process and cause death.

The **sublingual gland** is not often the seat of inflammation.

Chronic inflammation, leading to the formation of dense interstitial tissue, sometimes occurs in the salivary glands. This may occur by itself or follow an acute inflammation. **Tuberculous inflammation** of the parotid is not infrequent.[2]

The **excretory ducts** of the salivary glands may become inflamed from the presence of foreign bodies or of concretions formed in them. They may become occluded from the presence of calculi or as the result of inflammation, and may thus become widely dilated both in the main branches and in the finer ramifications. The dilatation of Wharton's duct to form larger and smaller cysts containing salivary fluid sometimes gives rise to very large and troublesome tumors which constitute one of the forms of *ranula*.[3]

TUMORS OF THE SALIVARY GLANDS.

Fibromata sometimes occur in the parotid; **chondromata, myxomata,** and **sarcomata,** including **fibrosarcomata** and **melanosarcomata,** have been described. A more common growth, however, is the **mixed tumor,** containing fibrous connective tissue, epithelium, cartilage, and cylindromatous portions (Fig 518). Similar neoplasms are occasionally dis-

[1] See *Herb, I. C.*, Jour. Infect. Dis., 1909, iv, 201; *Wollstein, M.*, Jour. Am. Med. Assn., 1918, lxxi, 639.

[2] Consult *Meslay* and *Parent*, Gaz. d. hôp., 1899, lxxii, 156 (bibl.); also *Wood, G. B.*, Univ. Pennsylvania Med. Bull., 1903, xvi. 368.

For bibliography of lesions of the salivary glands, see *Thorel*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 221. For a very complete survey from a surgical point of view, see *Heineke*, Deutsch. Chir., Stuttgart, 1913, Lief. xxxiii.

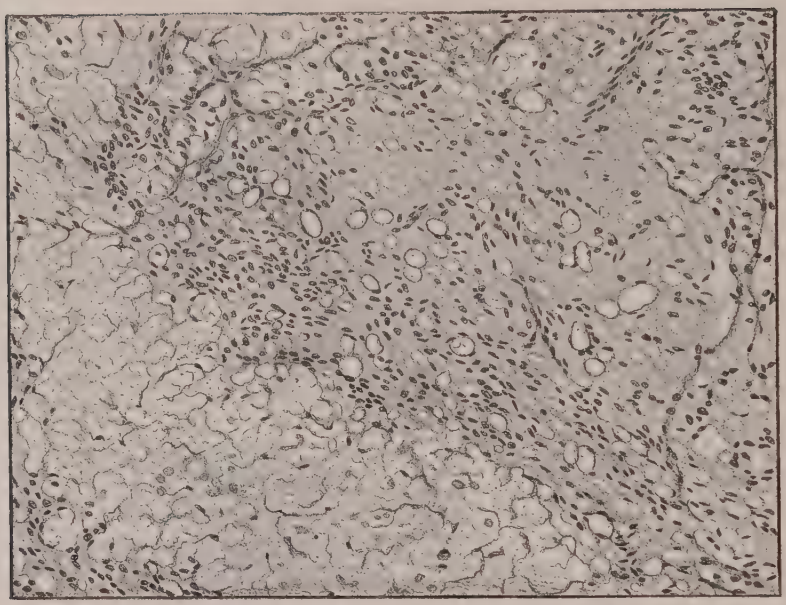


FIG. 518.—COMPLEX TUMOR OF PAROTID.
Containing fat and mucoid tissue and a few cellular areas not showing the gland type.

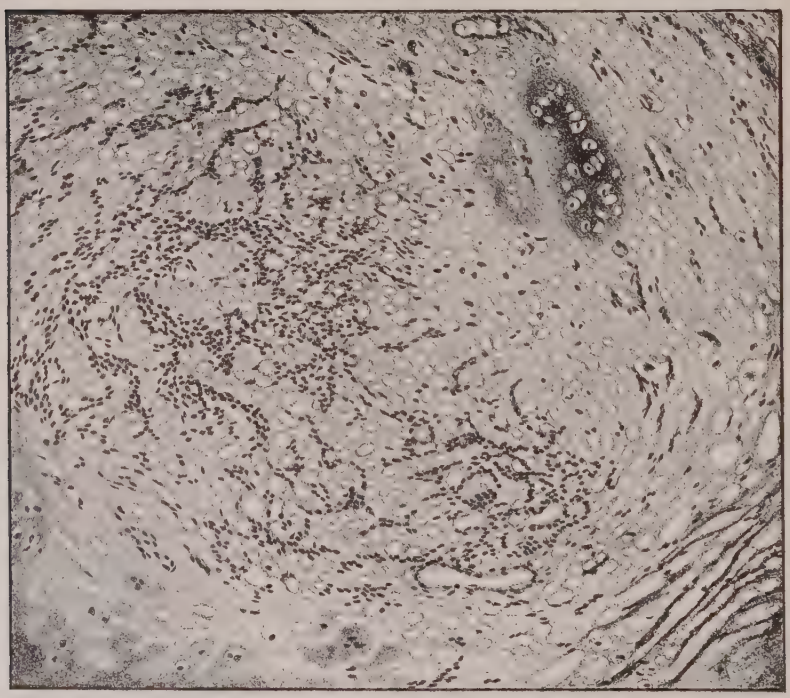


FIG. 519.—COMPLEX TUMOR OF PAROTID.
Containing cartilage, bone, and myxomatous and glandular tissue.

FIG. 520.—ADENOMA OF PAROTID.

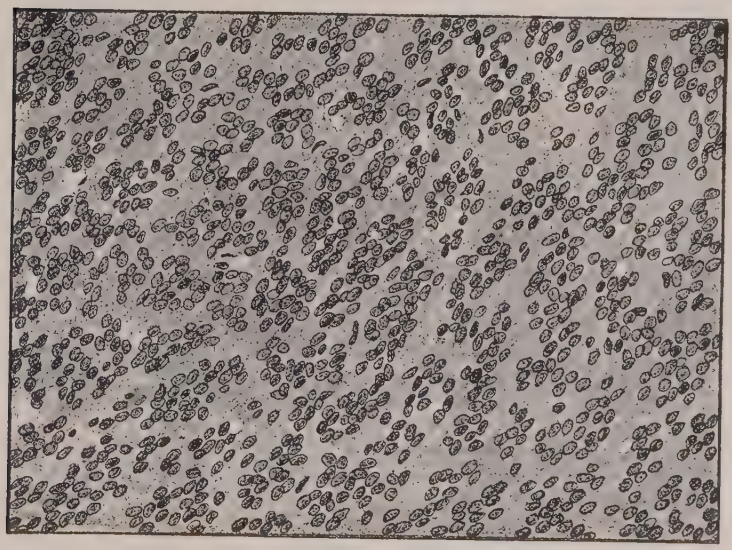


FIG. 521.—TUMOR OF PAROTID.

Composed of cellular areas embedded in mucoid tissue. While tumors of this type are unquestionably epithelial in nature, they very closely resemble the sarcomata.

covered in the submaxillary gland also. These complex or mixed tumors, which are sometimes called **adenochondromata** (Fig. 519), originate more frequently in the salivary glands than in any other part of the body, and are sometimes rendered still more complex in structure by the formation of cysts and by what has been usually regarded as an atypical glandular growth lending to them an adenomatous character (Fig. 520). Earlier studies upon these tumors led to the belief that a large proportion were endotheliomata[1] (see page 451); but more recent studies indicate that many cell types formerly interpreted as endothelium are actually epithelium (Fig. 521).[2]

Although it has been asserted[3] that the growths under discussion should be classed as basal-cell carcinomata, the more general opinion is that they are derived from congenital remnants of the glandular structures.[4] The majority are benign, malignant examples being exceptional.

Other benign growths of the salivary glands include **angioma**[5] and **rhabdomyoma.**[6]

Primary carcinoma and **squamous-cell epithelioma** are very rare.

The Pancreas.

Malformations and Displacements.

The pancreas may be entirely absent in acephalous and double monsters. The pancreatic duct may be double; it may open into the duodenum at some distance from the biliary duct, or into the stomach. The head of the pancreas may be unduly developed and sometimes even completely separated from the rest of the organ, opening into the duodenum with a duct of its own. The gland may be variously lobed and distorted. Occasionally there is a small accessory pancreas situated beneath the serosa of the duodenum or stomach.[7]

The pancreas is so firmly bound down that its position is not often changed. Sometimes, however, it is found pressed downward by tight lacing, displaced by aneurysms, or contained in umbilical and diaphragmatic herniæ.

ATROPHY, DEGENERATION, AND NECROSIS.

Atrophy of the pancreas may occur in old age and as a result of pressure from tumors or other adjacent structures, and may be associated with fatty infiltration. It occurs in a certain proportion of cases of diabetes mellitus.

[1] *Volkmann*, Deutsch. Ztschr. f. Chir., 1895, xli, 61; *v. Hansemann*, Ztschr. f. Krebsforsch., 1910, ix, 379, *Trendelenburg* and *Heineke*, Deutsche Chirurgie, Lief. 33. Stuttgart, 1886–1913.

[2] For a critical study of the mixed tumors of the salivary gland, see *Wood, F. C.*, Ann. Surg., 1904. xxxix, 57 (bibl.); *Wilson* and *Willis*, Am. Jour. Med. Sc., 1912, cxliii, 654; *Löwenstein*, Frankfurt., Ztschr. f. Path., 1910, iv, 187.

[3] *Krompecher*, Der Basalzellenkrebs, Jena, 1903, p. 204; and Zieglers Beitr., 1908, liv, 51.

[4] For an admirable series of studies along this line, see *Huntington*, *Schulte*, and *Carmalt*, Anatomy and Development of the Salivary Glands in the Mammalia, Studies in Cancer and Allied Subjects, George Crocker Special Research Fund, vol. iv, New York, 1913.

[5] *v. Haberer*, Arch. f. klin. Chir. (Langenbeck), 1910, xciii, 817 (bibl.). For a discussion of angioma with particular reference to tumors of the parotid in children, see, *Grulee*, Surg., Gynec., and Obst., 1906, ii, 31 (bibl.).

[6] *Prudden*, Am. Jour. Med. Sc., 1883, lxxxv, 438.

[7] For obliteration of pancreas and ducts with congenital obliteration of gall-ducts, see *Hess, A.*, Arch. Int. Med., 1912, x, 37.

Autodigestion of portions of the pancreas, *intra vitam*, has been described, and may, it is believed, lead to localized formation of fibrous tissue in the organ.[1]

Albuminous Degeneration may occur in acute infectious diseases. The organ may be red, swollen, and edematous. The most marked

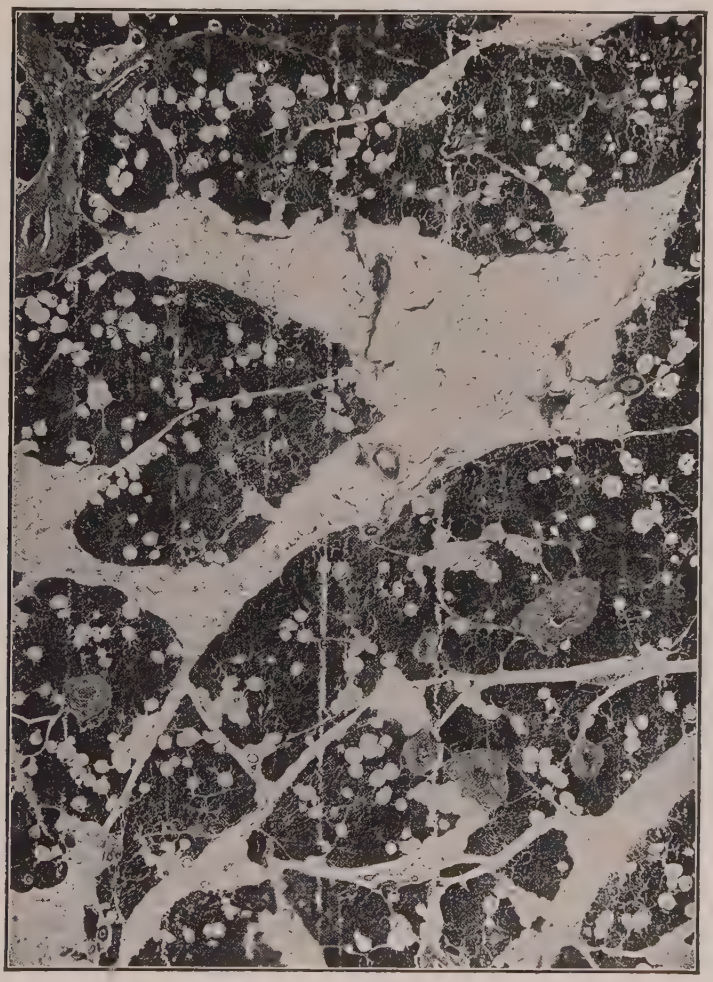


FIG. 522.—FATTY INFILTRATION WITH ATROPHY OF THE PANCREAS.

minute lesions are swelling and albuminous degeneration of the gland epithelium with hyperemia and interstitial edema.

Fatty Degeneration may follow albuminous degeneration and is most common in poisoning, especially by phosphorus.

Fatty Infiltration, which should be distinguished from fatty degeneration, consists in the accumulation of fat in the interstitial tissue of the

[1] *Chiari, H.*, Prag. med. Wchnschr., 1900, xxv, 29.

gland (Fig. 522). This when excessive may be associated with almost complete atrophy of the gland structures. Under these conditions the outline of the organ may be preserved, the fat being inclosed by the capsule. It occurs in obesity and in atrophy and fibrosis of the gland.

Amyloid Degeneration.—This usually occurs in connection with similar degeneration in other organs, and is confined to the walls of the blood-vessels and the interstitial tissue.

Fig. 523.—Fat Necrosis in the Mesentery.
From a case of acute hemorrhagic pancreatitis.

Hyaline Degeneration, involving and limited to the islands of Langerhans, has been described by Opie and others in diabetes without other marked lesions of the pancreas.[1]

Fat Necrosis.—This is a peculiar lesion of the fat tissue, most frequently seen about the pancreas or between its lobules, but sometimes in fat tissue in other parts of the body. White or yellowish nodules (Fig.

[1] *Opie, E. L.*, Jour. Exper. Med., 1901, v, 527; also Disease of the Pancreas, 2d ed., Philadelphia, 1910, on structure, function, and lesions of the pancreas with bibl. For development of the islands of Langerhans in human embryo, see *Pearce, R. M.*, Am. Jour. Anat., 1903, ii, 445. For morphology and physiology of these structures, see *Dewitt, L.*, Jour. Exper. Med., 1906, viii, 193. For hypertrophy of the islands of Langerhans, see *MacCallum, W. G.*, Am. Jour. Med. Sc., 1907, cxxxiii, 432, and *Cecil, R. L.*, Jour. Exper. Med., 1911, xiv, 500. For adenoma of islands of Langerhans, see *Cecil, R. L.*, Jour. Exper. Med., 1911, xiii, 595; and *LeComte, R.*, Jour. Med. Research, 1913, N. S. xxiv, 251.

523), varying from the size of a pin's head to that of a pea or larger, are seen embedded in the fat, the central portion being often soft and grumous. They are sometimes calcified and sometimes surrounded by a connective-tissue capsule. Microscopical examination shows necrosis, degeneration, and disintegration of the fat tissue (Fig. 524).

Fat necrosis is usually associated with lesions of the pancreas—hemorrhagic infiltration, necrosis, gangrene, and acute and chronic inflammatory processes. The lesion has been shown to be due to some ferment in the pancreatic secretion which splits the fat molecule into fatty acids, which may crystallize, and soluble substances; calcification is of later occurrence. Experimental studies have shown that fat necrosis can be induced by such operative procedures as direct the pancreatic secretion into fat tissue either immediately about the pancreas or elsewhere.[1]

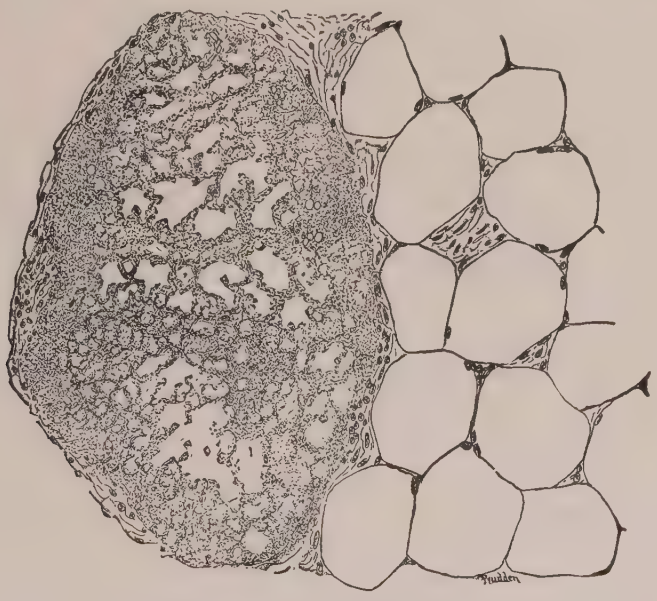


FIG. 524.—FAT NECROSIS IN THE PANCREAS.

HEMORRHAGE.

Hemorrhage into the substance of the pancreas may occur as the result of injury; in the hemorrhagic diathesis; in connection with valvular diseases of the heart or interference with the portal circulation; or in connection with extensive fatty degeneration, or with local necrosis, or with fat necrosis of the organ. Such hemorrhages may be minute or extensive. Several cases of sudden death are recorded in which the only discoverable lesion was an extensive hemorrhage into the substance of the gland and the tissue about it. The hemorrhage may be moderate

[1] For studies in fat necrosis with bibl., see *Opie*, Disease of the Pancreas, 2d ed., Philadelphia, 1910, also *Wells, H. G.*, Jour. Med. Research, 1903, N. S. iv, 70.

and limited to the pancreas, or it may extend into the subperitoneal tissue for a considerable distance.

Hemorrhage of the pancreas may be associated with acute inflammatory changes and with more or less extensive *gangrene* of the organ.[1]

INFLAMMATION. (Pancreatitis.)

Hemorrhagic Pancreatitis.—In this form of disease hemorrhage similar to that above described is associated with suppurative inflammation or gangrene or both. The gangrenous pancreas may be more or less encapsulated; it may be surrounded by pus. Hemorrhagic pancreatitis is often associated with fat necrosis.

The conditions leading to pancreatic hemorrhage and hemorrhagic pancreatitis are not yet fully clear, but in some cases at least the presence of intestinal juice or of bile and bacteria in the pancreatic duct is of importance. The frequent association of gall-stones in the ampulla with hemorrhagic pancreatitis is significant,[2] the obstruction by the stone leading to a regurgitation of bile up either the main pancreatic duct or one of the accessory ducts.

Suppurative Pancreatitis is not very common, and may be primary or due to the extension of a suppurative inflammation from adjacent or distant parts of the body. There may be a diffuse infiltration of the organ with pus cells or larger and smaller abscesses. The abscesses may open into the gastrointestinal canal or into the peritoneal cavity. The causes of primary suppurative pancreatitis are often obscure. It may accompany fat necrosis and hemorrhage and gangrene of the pancreas. It is probably usually due to bacterial invasion through the duct.

Various forms of bacteria have been found in the necrotic, hemorrhagic, and inflammatory lesions of the pancreas, but in most cases the significance of their presence is not clear, since necrotic and hemorrhagic foci may afford regions favorable to the lodgment and proliferation of microorganisms which are secondary invaders and whose lesions, if such be induced, are complicating and not primary.[3]

Chronic Interstitial Pancreatitis.—This lesion consists in an increase of interstitial connective tissue, which may be general or confined to some particular portion of the gland. The new-formed tissue may be interlobular or interacinar in distribution.

The organ is sometimes enlarged, sometimes smaller than normal. It is usually dense and hard; secondary atrophy of the parenchyma regularly occurs. It may be associated with chronic inflammatory processes in the vicinity of the organ, and obstruction of the pancreatic duct. It

[1] For a study of hemorrhagic necrosis of the pancreas, see *Opie* and *Meakins*, Jour. Exper. Med., 1909, xi, 561 (bibl.).

[2] For a study of the relationships between cholelithiasis and diseases of the pancreas, see *Opie*, Disease of the Pancreas, 2d ed., Philadelphia, 1910. For a study of experimental pancreatitis, see *Flexner, S.*, Univ. Med. Mag., 1901, xiii, 780; and Jour. Exper. Med., 1906, viii, 167; also *Flexner* and *Pearce*, Tr. Assn. Am. Phys., 1901, xvi, 348; also *Opie, loc. cit.*

[3] For a detailed consideration of acute hemorrhage, gangrene, and fat necrosis of the pancreas, with bibl., consult *Fitz, R. H.*, Tr. New York Path. Soc., 1889, p. 3. For later bibl. see *Warthin*, Philadelphia Med. Jour., 1898, ii, 1067; *Eve*, Brit. Med. Jour., 1915, i, 7; and *Opie, E. L.*, Diseases of the Pancreas, 2d ed., Philadelphia, 1910.

may accompany cirrhosis of the liver.[1] It regularly follows acute hemorrhagic pancreatitis, if the patient survive.[2]

Tuberculous Inflammation.—Larger and smaller tubercles and tuberculous cheesy nodules are occasionally found in the pancreas in connection with acute general miliary tuberculosis or with tuberculous inflammation in some other organ, particularly with that of adjacent lymph-nodes, the lungs, and the intestine.

Syphilitic Inflammation.—Chronic interstitial pancreatitis is frequently found in congenital syphilis of the new-born. The fibrous tissue is increased with atrophy of gland parenchyma, but the islands of Langerhans persist.[3] It is not definitely established whether or not a similar lesion may be caused by acquired syphilis. Gummata are very rare in the pancreas, but have been described in congenital syphilis in very young children.

TUMORS.[4]

Benign tumors of the pancreas are extraordinarily rare, and only a few have been described; these include **adenoma**[5] (Fig. 525), which sometimes originates in the islands of Langerhans, **fibroadenoma,**[6] and **fibroma.**[7] **Lipoma, myxoma,** and **chondroma** have been found.[8]

The most common neoplasm of the pancreas is **carcinoma,**[9] which makes up about 0.5 per cent. of all carcinomata. In two thirds of the cases the growth originates in the head of the gland, and most often from the ducts.

Sarcoma of the pancreas is a very rare tumor;[10] like carcinoma it most often involves the head of the gland. The growth may be of the small round-cell, spindle-cell, or polymorphous-cell variety. As with carcinoma,[11] even though large areas of the pancreas are involved many of the islands of Langerhans may be spared. The observation that even in wide-spread involvement of the gland there may be no diabetes[12] shows that the preservation of the islands of Langerhans certainly has something to do with the absence of sugar in the urine. Sarcoma may metastasize widely or not at all.

[1] See reference to *Lando*, Ztschr. f. Heilk., Abth. f. path. Anat., 1906, xxvii, 1.

[2] For experimental evidence of this, see *Whipple, Chaffee,* and *Fisher*, Bull. Johns Hopkins Hosp., 1910, xxi, 339.

[3] For a study of the pancreas in congenital syphilis, see *Pearce*, Am. Med., 1903, vi, 1020.

[4] For a general discussion of tumors of the pancreas and bibl., see *Heiberg*, Die Krankheiten des Pankreas, Wiesbaden, 1914, p. 152 ff.

[5] *Heiberg*, Centralbl. f. allg. Path., 1911, xxii, 532 (bibl.); *Cecil*, Proc. New York Path. Soc., 1910, x, 135; *v. Beust*, Virchows Arch., 1915, ccxix, 191; *Rollett*, Frankfurt. Ztschr. f. Path., 1912, x, 268 (bibl.); *Helmholtz*, Bull. Johns Hopkins Hosp., 1907, xviii, 185 (bibl.); *Nicholls*, Jour. Med. Research, 1902, N. S. iii, 385 (bibl.); *Koch*, Virchows Arch., 1914, ccxvi, 25.

[6] *Biondi*, cited by Heiberg, Die Krankheiten des Pankreas, p. 179.

[7] *Körte*, Deutsch. med. Wchnschr., 1909, xxxv, 2153.

[8] *Kaufmann*, Lehrbuch d. spez. Path., Berlin, 1911, i, 651.

[9] *Heiberg*, Centralbl. f. allg. Path., 1911, xxii, 233; *Baldwin*, Philadelphia Med. Jour., 1900, vi, 1195 (bibl.); *Leriche*, Lyon chir., 1910, iv, 261 (French bibl.); Arch. f. klin. Chir., 1910, xcii, 1048.

[10] *Kakels*, Am. Jour. Med. Sc., 1902, cxxiii, 471 (bibl.); *Schirokogoroff*, Virchows Arch., 1908, cxciii, 333 (bibl.); *Halász*, Wien. klin. Wchnschr., 1908, xxi, 1807 (bibl.); *Constantini*, Tumori, 1911–12, i, 735 (bibl.); *Boyd*, Jour. Am. Med. Assn., 1901, xxxvi, 1461 (bibl.).

[11] *Herxheimer*, Verhandl. d. deutsch. path. Gesellsch., 1904, vii, 215.

[12] *Schirokogoroff*, Virchows Arch., 1908, cxciii, 395. For another view, see *Braunstein*, Klin. Woch., 1924, iii, 788.

Cysts of the pancreas,[1] which are rather uncommon, are usually divided into three classes: 1. *Retention cysts*, due to obstruction of the duct of Wirsung from within by a concretion or from without by gall-stones, neoplasms, etc., may involve the entire passage in a uniform dilatation. Or the smaller tributary ducts alone may be dilated, perhaps from the presence of chronic fibrotic changes in the organ, so as to form a number of small cysts. The wall of a retention cyst is fibrous and may or may not have an epithelial layer. The contents may exhibit any or all of the pancreatic ferments or none of them.

2. *Pseudocysts* (*apoplectic cysts*).—These are the result of trauma,[2] or of acute hemorrhagic pancreatitis. They project from the surface of the gland (*peripancreatic*) or, less commonly, are situated within its substance (*endopancreatic*). As in the preceding variety, the wall is fibrous and may or may not have an epithelial lining. The contents are often blood stained and usually lacking in ferments.

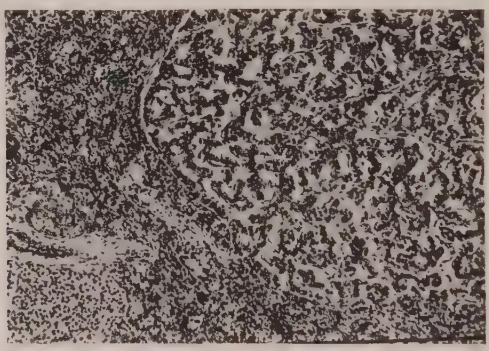


Fig. 525.—Adenoma of Pancreas. × 100.

3. *Proliferative Cysts.*—These include such lesions as *cystadenoma*,[3] *sarcoma*, either multiple or papilliferous, *cystic carcinoma*, etc. Their contents may be hemorrhagic and may exhibit any or all of the pancreatic ferments.

To these three varieties may be added **echinococcus** cysts.[4]

Concretions of carbonate and phosphate of lime are frequently found in the pancreatic ducts. They are usually multiple, small, whitish, smooth, or rough and of irregular shape. Sometimes, however, they reach a diameter of more than an inch. They consist chiefly of calcium phosphate and carbonate. Besides these free concretions the walls of the ducts are sometimes encrusted with salts of lime. Such concretions may produce dilatation of the pancreatic ducts and large cysts, or more rarely abscesses.

Foreign Bodies.—Gall-stones sometimes find their way into the pancreatic duct. Ascarides have been found in the ducts in a considerable number of cases.

[1] *Willis* and *Budd*, Surg., Gynec., and Obst., 1915, xx, 688 (bibl.); *Heiberg*, Die Krankheiten des Pankreas, Wiesbaden, 1914, p. 130; *Friedenwald* and *Cullen*, Am. Jour. Med. Sci., 1926, clxxii, 313 (bibl.).

[2] *Graf*, München. med. Wchnschr., 1910, lvii, 2529 (bibl.).

[3] *Roman*, Virchows Arch., 1912, ccix, 234 (bibl.).

[4] *Hanser*, Beitr. z. klin. Chir. (Bruns), 1912, lxxvii, 360 (bibl.).

CHAPTER VIII.

THE LIVER.

Malformations.

Congenital malformations of the liver are not common and are of little practical importance. The organ may be entirely wanting; it may be very small;[1] the lobes may be diminished or increased in number; its form may be altered, so that it is rounded, flattened, triangular, or quadrangular. The gall-bladder or gall-ducts may be absent; the ductus choledochus may be double, both ducts emptying into the duodenum, or one emptying into the duodenum, the other into the stomach. The single ductus choledochus may also empty into the stomach. Owing to abnormal openings in the diaphragm or the abdominal parietes, the liver may suffer displacement upward or forward. In congenital transposition of the viscera the liver is found on the left side, the stomach and spleen on the right side.

Small, isolated bodies, having the same structure as the liver, have been a few times found in the suspensory ligament, on the surface of the gall-bladder, and in the lesser omentum.

Acquired Changes in Size, Form, and Position.

As a result of tight lacing very marked changes are sometimes produced in the shape of the liver. By the narrowing of the base of the thorax the organ is compressed from side to side, and its convex surface is pressed against the ribs. In consequence of this there are found ridges and furrows on its convex surface. In consequence also of the circular constriction, a part of the right, and usually a part of the left lobe, become separated by a depression (Fig. 17). Over this depressed and thinned portion of the liver the capsule is thick and opaque. In extreme cases the depression and thinning reach such an extent that there is only a loose, ligamentous connection between the separated portion and the liver.

A series of depressions are sometimes found on the upper surface of the right lobe of the liver, running from front to back, apparently caused by folds of the organ. These folds are most often found in patients who have suffered from severe dyspnea before death; but in some instances they may be congenital.[2]

Structural alterations in the liver may induce changes in its size and shape. It may be increased in size by tumors, hydatid cysts, abscesses, fatty and amyloid degeneration, and congestion, and sometimes by cirrhosis, etc.

It may be diminished in size by atrophy, by cirrhosis, by acute parenchymatous degeneration, etc.

Changes in the position of the liver are produced by alterations in its size, by pressure downward from the thoracic cavity and upward from the abdomen, by the constriction of tight lacing, by tumors or circumscribed serous exudation between the liver and diaphragm, by curvature of the spine.

The liver is readily turned, by pressure from above or below, on its transverse axis. The transverse colon may be fixed above the liver so as to push it backward, downward, and to the right. There are a few cases recorded of dislocated and movable livers. These occurred in women who had borne children and whose abdominal walls were lax. With ascites it is not uncommon to find the liver quite movable.[3]

WOUNDS, RUPTURE, AND HEMORRHAGE.

Wounds of the liver may induce hemorrhage, which, if life continue, is followed by inflammation. Serious wounds of the liver are usually

[1] *Zypkin*, Virchows Arch., 1908, cxciv, 63.
[2] *Chiari*, Verhandl. d. deutsch. path. Gesellsch., 1899, ii, 107.
[3] For displacements of the liver, see *Graham*, Tr. Assn. Am. Phys., 1895, x, 258 (bibl.).

fatal, but recovery may occur even after the destruction of a considerable portion of the organ.

Rupture of the liver may be produced by severe direct contusions or by falls. It may be produced in children by artificial delivery. The rupture usually involves both the capsule and a more or less considerable portion of the liver tissue. It is commonly accompanied by large hemorrhage, and is usually fatal.

Hemorrhage.—Extravasations of blood in the substance of the liver, or more frequently beneath the capsule, may be found in new-born children after tedious or forcible labors. In adults, hemorrhage, except as the result of injury, is uncommon. Extravasations of blood are sometimes seen in malignant malarial fevers, especially in tropical climates; in scurvy, purpura, and phosphorus poisoning; and bleeding may occur in and about soft tumors, abscesses, and echinococcus cysts. It may also occur as a result of thrombosis of the hepatic vein.

ANEMIA AND HYPEREMIA.

Anemia of the liver may be general or partial. It may be due to general anemia or to local disturbances of the circulation, such as swell-

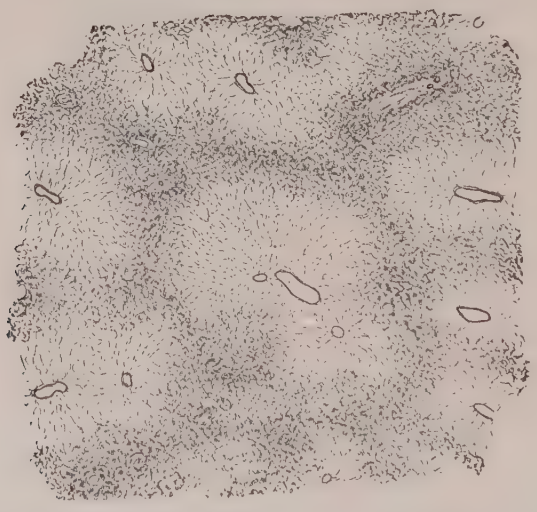


FIG. 526.—CHRONIC CONGESTION OF THE LIVER—"NUTMEG LIVER."

The liver cells are completely atrophied except in the peripheries of the lobules. The central portions of the lobules, which in the fresh organ are darker than the periphery, are lighter in the preserved specimen from which this section was cut, because the hemoglobin has been dissolved out of the red blood-cells.

ing of the cells in parenchymatous or other degeneration, pressure of tumors, etc. The organ appears pale, often of slightly yellowish or brownish color. It may be harder than usual, and smaller.

Hyperemia of the liver is either an active or a passive process. In health the amount of blood in the liver varies at different times, being regularly increased during the process of digestion. When the digestive

process is unduly influenced by the ingestion of spirits, spices, etc., the hyperemia assumes abnormal proportions, and when this is often repeated it may lead to structural changes in the organ. Severe contusions over the region of the liver sometimes cause a hyperemia, which may result in suppurative or in productive inflammation. In hot climates and in malarious districts active and chronic hyperemia of the liver are frequent and often incite structural lesions. In scurvy, also, the liver is sometimes congested. Cessation and suppression of the menses and of hemorrhoidal bleeding may be followed by hyperemia of the liver. In all these varieties of active congestion the liver is enlarged, and of a deep red color, and blood flows freely from its cut surface.

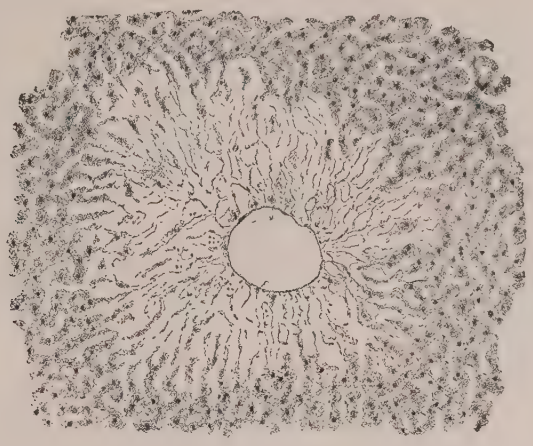


FIG. 527.—CHRONIC CONGESTION OF THE LIVER.

Showing a single lobule. The capillaries about the central vein are widely distended with blood—decolorized; the liver cells on the borders nearest the dilated capillaries show various phases of pressure atrophy.

Passive congestion of the liver is produced by an obstruction to the current of blood in the hepatic veins. Valvular diseases of the heart, emphysema and fibrous induration of the lungs, large pleuritic effusions, intrathoracic tumors, angular curvature of the spine, aortic aneurysms pressing on the vena cava, and constrictions of the vena cava and of the hepatic veins, may all lead to a chronic hyperemia of the liver. In such cases, since the congestion affects principally the hepatic veins, we find the center of each acinus congested and red, while its periphery is lighter in color. This gives to the liver a mottled or nutmeg appearance (*nutmeg liver*) (Fig. 526). The liver cells in the center of each acinus are frequently colored by little granules of red or black pigment, and the cells at the periphery become fatty, so that the nutmeg appearance is still more pronounced. A liver in this condition is usually of medium size, but may be smaller or larger than normal.

When the congestion is long continued the veins at the center of each acinus may become permanently dilated, and the hepatic cells in their meshes become atrophied (Fig. 527 and 528), so that the center of each

acinus consists only of dilated capillaries or of these and new connective tissue; or the dilatation and atrophy of the liver cells may, in circumscribed portions of the organ, involve the entire acinus. Whether the atrophy of the cells is due entirely to pressure or possibly in part to lack of nutrition owing to the sluggish blood-current in the vessels, is not yet clear. In long-continued congestion the liver is usually small and hard—cyanotic induration—and may be rough or uneven on the surface; but it is sometimes enlarged. The peculiar nutmeg appearance may be very well marked, or it may not be evident, the organ being of a dark-red color.[1]

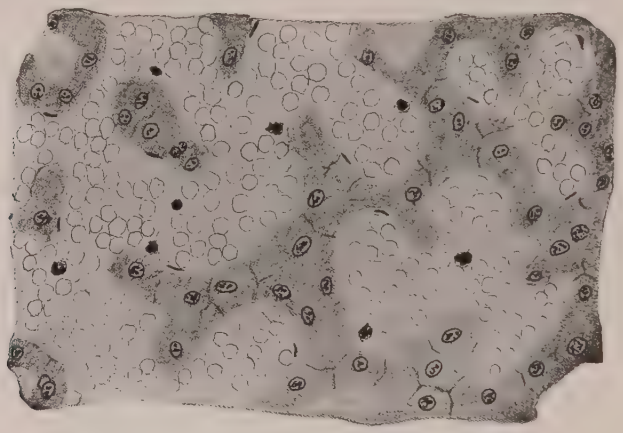


FIG. 528.—CHRONIC CONGESTION OF THE LIVER.
Showing atrophy of the liver cells.

LESIONS OF THE HEPATIC VESSELS.

THE HEPATIC ARTERY.

The hepatic artery is in rare cases the seat of aneurysms which may attain a large size. Such aneurysms may displace the liver tissue, may compress the bile ducts so as to cause jaundice, and may rupture into the stomach or abdomen.

Owing to its abundant anastomoses, emboli of the branches of the hepatic artery usually induce no marked lesions, but they sometimes result in single or multiple anemic infarcts.[2]

THE PORTAL VEIN.

Thrombosis, Embolism, and Inflammation.—*Thrombosis* of the branches of the portal vein may be produced by weakening of the circulation from general debility—*marantic thrombi;* by pressure on the vessel from without, as in cirrhosis, chronic peritonitis, tumors, gall-stones, dilatation of the bile ducts, etc.; by injury; by the presence of foreign materials within the vessel; and as a result of inflammation, especially

[1] For another view of chronic passive congestion of the liver, see *Mallory, F. B.*, Jour. Med. Research, 1911, N. S. xix, 455.

[2] For a critical summary of recorded cases of anemic infarcts of the liver, see *Baldwin, F. A.*, Jour. Med. Research, 1902, N. S. iii, 431. For a study of experimental closure of the hepatic artery and the gall-ducts, see *Tischner, R.*, Virchows Arch., 1904, clxxv, 90.

syphilitic, of its wall—phlebitis—or of embolus. The thrombus may form in the vessels in the liver or be propagated into them from without. It may partially or entirely occlude them. The clot may become organized as a result of endophlebitis, and a permanent occlusion of the vessel ensue. If the clot be a *simple*, non-irritating one, leading to occlusion, the consequences are usually more marked in the abdominal viscera than in the liver itself. The branches of the hepatic artery usually form sufficient anastomoses to nourish the liver tissue and prevent its necrosis even in complete occlusion of the portal vein; and if occlusion occur slowly, the organ may continue to perform its functions, though the production of bile is diminished, the amount formed by the liver depending directly upon the blood flow through the organ.[1] But this obliterative form of thrombosis is usually attended by ascites, enlargement of the spleen, and dilatation of the abdominal veins, and sometimes by hemorrhage from the stomach and intestines.

In another class of cases, in addition to the local and mechanical effects, the thrombus may be infectious; then there are necrotic changes and suppurative inflammation in the walls of the vessels or in the liver tissue about them. The thrombi are apt to soften and break down, and the fragments may be disseminated through the smaller trunks of the portal vein. In this way, by the distribution through the smaller vessels of a disintegrated thrombus from a large trunk, or by the introduction into the branches of the portal vein of purulent or septic material from some of the abdominal viscera or from wounds, multiple foci of purulent inflammation in the portal vein, and multiple abscesses involving the liver tissue, may be produced. In many cases the presence of bacteria may be detected in the inflammatory foci.

These soft thrombi of the portal vein and the accompanying pylephlebitis and abscess are induced in a variety of ways. Ulceration of the appendix, intestines and stomach, abscesses of the spleen, inflammation of the mesentery and mesenteric glands, inflammation and ulceration of the bile-ducts from gall-stones, inflammation of the umbilical vein in infants, may all induce local thrombi, which may be propagated to the portal vein or may give rise to purulent or septic emboli. Two cases are recorded in which a fish-bone in the portal vein induced suppurative inflammation in that vessel.[2]

In infants inflammation of the umbilical vein may induce not only inflammation of the portal vein and abscesses in the liver, but multiple abscesses in various parts of the body, and acute peritonitis may follow.

Infarcts.—Infarcts of the liver seldom form, owing to the abundant anastomosis of its blood-vessels. But under exceptional conditions, as we have seen, *anemic infarcts* may occur as the result of the closure of the hepatic artery or of small branches of the portal vein. There may then be a larger or smaller mass of dead liver tissue surrounded by a zone of congestive or inflammatory reaction (Fig. 529). Occasionally also, owing usually to the occlusion of branches of the portal vein, lim-

[1] *Voegtlin, C.*, and *Bernheim, B. M.*, Jour. Pharmacol. and Exper. Therap., 1910, ii, 455.

[2] For a study of primary portal thrombosis, see *Lewis* and *Rosenow*, Arch. Int. Med., 1909, iii, 232 (bibl.).

ited areas of liver tissue may suffer disturbance of the circulation leading to atrophy of the liver cells and the formation of fibrous tissue. This condition has been called *hemorrhagic atrophic infarction.* It is apparently rather localized atrophy of the liver than true infarction.

It is probable that the rare occurrence of hepatic infarcts is closely

FIG. 529.—INFARCTION OF THE LIVER.
The infarcts, multiple and large, are due to extensive thrombosis of branches of the portal vein.

dependent in most instances upon the development of local thrombosis or embolism, which commonly do not lead to infarction, together with general disturbances of the circulation which prevent the re-establishment of equilibrium in the hepatic vessels.[1]

[1] For a study of liver infarcts, see summary by *Baldwin*, Jour. Med. Research, 1902, N. S. iii, 431; also *Steinhaus*, Deutsch. Arch. f. klin. Med., 1904, lxxx, 364.

Rupture of the Portal Vein, with fatty degeneration of its walls, has occurred in a few instances.

Chronic Endophlebitis, with atheroma and calcification, may occur in the walls of the portal vein, giving rise to thrombosis.

Dilatation of the Portal Vein, either uniform or varicose, may occur in various parts of the vessel or its branches. It may be caused by destruction of the liver capillaries in cirrhosis, or by occlusion of the vein by thrombi, tumors, etc.

The Hepatic Veins.

The hepatic veins present lesions similar to those of the portal vein and its branches, but they are much less frequent. The veins may be dilated by obstruction to the passage of venous blood into the heart. They may be the seat of acute and chronic inflammation, and soft thrombi and suppurative inflammation may be produced by abscesses in the liver. Rarely there is a localized obliterating phlebitis in the hepatic vein followed by chronic congestion, interstitial inflammation, and thrombosis.[1] When the obstruction of the hepatic veins is rapid, the liver enlarges slowly and is very tender. Ascites, cyanosis, and in some cases an acidosis have been noted.[2]

ATROPHY OF THE LIVER.

Atrophy of the liver may affect the entire organ or be confined to some part of it. General atrophy may occur in old age as a senile change, or may be induced by starvation or chronic exhausting diseases. The organ is diminished in size and is usually firm; and the acini appear smaller than usual. Microscopically, the change is seen to be due to a diminution in size of the liver cells, and hand-in-hand with this there occurs frequently an accumulation of pigment granules within the atrophied cells. The cells may entirely disappear over circumscribed areas, leaving only shrivelled blood-vessels and connective tissue; or, in some cases, there may be an increase of connective tissue associated with the atrophy of the cells. When much pigment is formed in the cells the lesion is often called *pigment atrophy.*

Essentially the same changes may occur in circumscribed portions of the liver, as the result of pressure from new connective tissue in cirrhosis, from tumors, hydatids, amyloid degeneration, gall-stones, etc. In atrophy from pressure the liver cells are apt to become very much flattened and squeezed together as they diminish in size.

NECROSIS.

Necroses in the liver may occur under various conditions and in many forms.[3]

Minute areas of necrosis of liver cells, *focal necrosis* (page 238), are

[1] Consult, for obliterating phlebitis of the main trunks of the hepatic vein as a cause of death, *Chiari, H.*, Zieglers Beitr., 1899, xxvi, 1 (bibl.).

[2] *Thompson, T.*, and *Turnbull, H. M.*, Quart. Jour. Med., 1912, v, 277; *Jacobson, V. C.*, and *Goodpasture, E. W.*, Arch. Int. Med., 1918, xxii, 86.

[3] For a study of necroses of the liver, see *Mallory, F. B.*, Jour. Med. Research, 1901, N. S. i, 264.

found irregularly scattered through the organ in various acute infections, and may be artificially induced in animals by the injection of bacteria, diphtheria toxin, or vegetable toxins such as ricin and abrin.[1]

More extensive necroses of liver cells, especially about the central vein, frequently occur, usually in acute infectious diseases—diphtheria, endocarditis, lobar pneumonia, peritonitis, cerebrospinal meningitis.[2] This has been called *central necrosis*.

Necrosis in the liver may, however, be limited to the peripheral zone of the lobule, *peripheral necrosis*. This condition has been described in a few instances, especially in connection with eclampsia.

Finally, the necrosis of parenchyma cells in the liver may be limited to the middle zone of the lobule, "*midzonal necrosis*."

In most of these forms of so-called "zonal necrosis"[3] bacterial toxins or infections appear to be the chief determining factor.

Many of the necroses of the liver are doubtless due to the action of bacteria or bacterial toxins. The focal forms may be determined by the local growth of bacteria, by the occlusion of capillaries by swollen and proliferated endothelial cells, as in typhoid fever, or by fibrinous or agglutinative thrombi.

The reason for the topography of the lesion in the various forms of "zonal necrosis," and the relation of these necroses to certain phases of eclampsia, chloroform poisoning, and acute yellow atrophy of the liver have not yet been definitely determined.

It has been shown[4] that by the injection into animals of hemagglutinative substances contained in various cytolytic immune sera, agglutinative thrombi may form in the capillaries and smaller branches of the portal vein, leading to necrosis of the liver. The position and extent of these areas of hyaline necrosis vary with the amount of the serum administered. They are mostly superficial, and may be small and focal or involve nearly all the parenchyma of the lobule, except that in the vicinity of the portal spaces.

It has been shown,[5] also, that similar lesions may follow the injection of hemagglutinins of bacterial origin. In these areas of hyaline necrosis the liver cells stain poorly with eosin; the nuclei do not stain and may be seen only as faint outlines, or may be shrunken.

The occurrence has been described of multiple circumscribed necrotic and atrophic foci in the liver not associated with local infective processes and without marks of inflammation or connective-tissue hyperplasia. These are associated with stasis in the blood and bile capillaries, and local portal sclerosis; and the areas contain bile pigment. The lesion is most marked about the central vein, and may vary in extent. It is associated with jaundice. The condition is diffuse in the liver, often running in streaks which merge into normal liver tissue. Thus the liver becomes tough, pale, and bile-stained, with obscured markings. The liver cells in the affected areas apparently lose their cytoplasm, leaving a well-preserved outline, and may contain fat.

For this lesion the designation *multiple non-inflammatory necrosis of the liver with jaundice* has been suggested.[6]

[1] *Flexner, S.*, Johns Hopkins Hosp. Rep., 1897, vi, 259; *Mallory, F. B.*, Jour. Exper. Med., 1898, iii 611.

[2] *Mallory, F. B.*, Jour. Med. Research, 1901, N. S. i, 264.

[3] For a study of "zonal necroses" of the liver, see *Opie, E. L.*, Jour. Med. Research, 1904, N. S. vii, 147.

[4] *Pearce, R. M.*, Jour. Med. Research, 1904, N. S. vii, 329; 1906, N. S. ix, 541.

[5] *Pearce and Winne*, Amer. Jour. Med. Sc., 1904, cxxviii, 669.

[6] *Oertel, H.*, Jour. Med. Research, 1904, N. S. vii, 75; Jour. Exper. Med., 1906, vii, 103, and Berl. klin. Wchnschr., 1912, xlix, 2019. For a study of changes in necrotic cells in cytolysis in the liver and elsewhere, see *Symmers, D.*, Jour. Exper. Med., 1907, ix, 64.

Experimental work has shown[1] that chloroform anesthesia in animals repeated on several successive days induces fatty degeneration or hyaline necrosis or both, of the liver cells in the central portion of the lobules. It has been found,[2] also, that animals may recover from the chloroform liver necroses with complete restitution of the cells after two or three weeks.

The acute degenerations of the liver occurring in eclampsia, in which condition chloroform is often administered, require careful scrutiny in view of the striking lesions of necrosis induced by chloroform alone.

DEGENERATION.

Albuminous Degeneration.—In the infectious diseases and in certain cases of acute anemia and phosphorus poisoning, the liver is swollen and, on section, of a dull yellowish gray color, looking as if it had been boiled. It contains less blood than usual, and the outlines of the lobules are indistinct. Microscopical examination shows the lesion to consist of a swelling of the liver cells and an accumulation in them of moderately refractile, finer and coarser albuminous granules. These granules may disappear and the cells return to their normal condition, or fatty degeneration may follow. Fatty and parenchymatous degenerations are often associated.

Acute Yellow Atrophy (Acute Parenchymatous Degeneration).—This rare condition is characterized anatomically by a rapid diminution in the size of the liver as the result of a granular and fatty degeneration, necrosis, and disintegration of the liver cells. It is frequently associated with the clinical condition called *icterus gravis*. The liver, sometimes within a few days, may be reduced to one-half its normal size. On opening the abdominal cavity the organ may be found lying, concealed by the diaphragm, close against the vertebral column. The amount of diminution and the general appearance of the affected organ depend to a considerable extent upon its previous condition—*i.e.*, whether or not it was the seat of other lesions—as well as upon the duration of the process and the degree of degenerative change. In general, if the lesion is well marked, the liver is small, flabby—sometimes almost fluctuating—and the capsule wrinkled. On section the cut surface may show but little trace of lobular structure, but present an irregular mottling with gray, ochre-yellow, or red; sometimes one, sometimes another color preponderating.

Microscopical examination shows varying degrees of degeneration and destruction of the liver cells. Most evidently in those parts which have a grayish appearance, the outlines of the cells are preserved and the protoplasm is filled with larger and smaller granules. In the yellow portions the outlines of the liver cells may be preserved, and they may contain varying quantities of larger and smaller fat droplets and granules of yellow pigment. Or the cells may be necrotic or disintegrated, and in their place be irregular collections of fat droplets, hyaline material, pigment granules, red and yellow crystals, and detritus, only the connective

[1] *Howland, J.*, and *Richards, A. M.*, Jour. Exper. Med., 1909, xl, 344; *Opie, E. L.*, ibid., 1910, xii, 367; *Cragin, E. B.*, and *Hull, E. T.*, Jour. Am. Med. Assn., 1911, lvi, 5; and *Fraser, A.*, Am. Jour. Med. Sc., 1916, cli, 202.

[2] *Whipple, G. H.*, and *Sperry, J. A.*, Bull. Johns Hopkins Hosp., 1909, xx, 278.

tissue and blood-vessels of the original liver tissue remaining (Fig. 530). The red areas may show nearly complete absence of liver cells and cell detritus, and sometimes irregular rows of cells which are variously interpreted as being new-formed gall-ducts or proliferated liver cells, marking a reparative process which may be extensive.[1] In these areas it appears to be, in part at least, the blood contained in the vessels which imparts the red color. Sometimes the interstitial tissue is infiltrated with small spheroidal cells resembling leucocytes. Crystals of leucin and tyrosin are sometimes found intermingled with the cell detritus. In some cases the liver is not diminished in size. In early stages it may even be larger than normal.

These lesions of the liver are frequently associated with enlargement of the spleen and parenchymatous degeneration of the kidney and of the

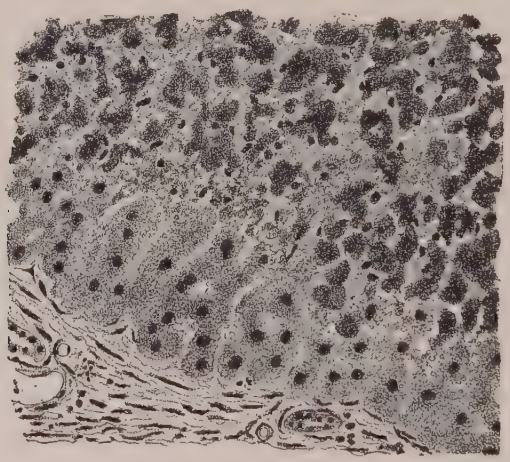


Fig. 530.—Acute Yellow Atrophy of the Liver.
The liver cells in the periphery of the lobule are little changed; those toward the center are largely destroyed.

heart muscle. Multiple hemorrhages may occur in the gastrointestinal canal, kidneys, bladder, and lungs. There is frequently marked jaundice.

The condition above described as acute yellow atrophy of the liver sometimes occurs in persons previously apparently well, but may accompany infectious diseases—typhoid fever, diphtheria, puerperal infection, etc.—and may be seen in eclampsia and pernicious vomiting in pregnancy. While the nature of the condition is not well understood it seems probable that the lesion is essentially a necrosis and degeneration resulting from toxic substances produced either in bacterial infection or through faulty cell metabolism and followed by more or less pronounced autolysis by the ferments resident in the liver cells. The fatal nature of

[1] For a study of regenerative changes in the liver after acute yellow atrophy, see *MacCallum, W. G.* Johns Hopkins Hosp. Rep., 1902, x, 375; also *Pearce, R. M.*, Jour. Med. Research, 1906, N. S. x, 99. See, also, for repair of liver, *Muir, R*, Jour. Path. and Bacteriol., 1908, xii, 287; and *Milne, L. S.*, Proc N. Y. Path. Soc., 1909, ix, 90.

the disease is probably dependent more upon the destruction of the liver cells than upon the exogenous inciting infection or toxemia. It is probably erroneous to consider the lesions of the liver described under the name of acute yellow atrophy as marking a single disease process.

As to the details of the pathogenesis of this condition, opinions differ, and the whole subject is in urgent need of more exact research.

In the forms of this liver lesion which mark the toxemia of pregnancy, whether these be clinically manifested in eclampsia, pernicious vomiting of pregnancy, or other well marked abnormal conditions, there appears to be a disturbance of nitrogenous metabolism in the liver, associated with the characteristic rapid destruction of the parenchyma.[1] Undoubtedly, however, some of the chemical abnormalities described as characteristic may be, in part at least, due to the accompanying inanition.[2]

It should be borne in mind, finally, that while acute yellow atrophy of the liver has been regarded as an especially fatal lesion, there is abundant clinical and morphological evidence that various grades of the lesion may occur and that recovery from many forms, with regeneration of liver tissue, is not uncommon.[3]

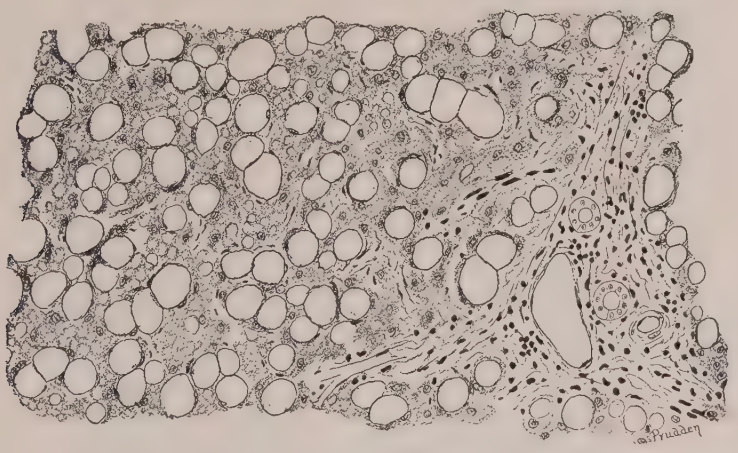


FIG. 531.—FATTY INFILTRATION OF LIVER.

Portion of the periphery of a lobule, showing many liver cells distended with a single large drop of fat, while between these are liver cells with small fat droplets and others flattened by pressure. In this section, hardened by alcohol, the fat has been dissolved, leaving clear spaces.

Experimental Studies.—The results of the experimental production in animals of lesions comparable with those of acute yellow atrophy in man are very suggestive.[4] It has been found that after the relatively slight injury of the liver parenchyma induced by repeated doses of chloroform in dogs, the injection of Bacillus coli—not itself especially virulent for these animals—may be followed by changes in the liver which neither the chloroform (page 827) nor the bacteria alone can induce. For under these conditions it appears that the liver cells may be largely destroyed by

[1] For discussion and bibl., see *White*, Boston Med. and Surg. Jour., 1908, clviii, 729.

[2] *Underhill, F. P.*, and *Rand, R. F.*, Arch. Int. Med., 1910, v, 61.

[3] For forms of acute yellow atrophy in the toxemia of eclampsia and other disturbances of pregnancy, see *Strauss*, Am. Jour. Obst., 1906, liii, 145 (bibl.); *Ewing, J.*, ibid., 1905, li, 145; and Proc. Path. Soc., Philadelphia, 1910, xiii, 65. For acute yellow atrophy in children, see *Philips, J.*, Am. Jour. Med. Sc., 1912, cxliii, 177 (bibl..); also *Graham, E. A.*, Jour. Exper. Med., 1912, xv, 307.

[4] *Opie, E. L.*, Jour. Exper. Med., 1910, xii, 367.

necrosis, the remainder being fatty, while evidence of reparative changes—new fibrous tissue and new-formed gall-ducts, such as are often seen in acute yellow atrophy in man—is strikingly shown. In view of these experiments attention has been called to the possibility that some of the lesions of the toxemia of pregnancy and acute yellow atrophy in man may in fact be due to the action of bacteria or their poisons on liver cells already vulnerable from metabolic or other forms of intoxication.

Fatty Infiltration.—In the normal human liver there is usually a certain amount of fat in the liver cells, and this amount varies considerably under different conditions.

The gross appearance of pathological fatty livers varies a good deal, depending upon the amount and distribution of fat and its association with other changes. If the lesion is uncomplicated and considerable, the organ is increased in size, the edges are rounded, the consistence is firm, the color yellowish, and the cut surface greasy. The lobules are enlarged and their outlines indistinct, and the blood content is diminished. The liver is increased in weight. The lesion may be uniform throughout the organ or it may occur in patches. In the latter case the liver has a mottled appearance, irregular yellowish patches alternating with the brownish red, unaffected portions.

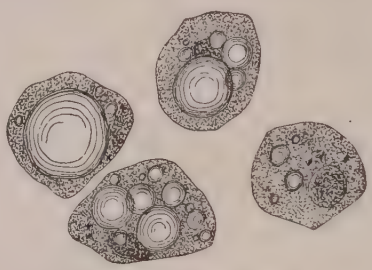


Fig. 532.—Fatty Infiltration of Liver Cells.

Fatty infiltration is often associated with chronic congestion (*nutmeg liver*), with cirrhosis, and with amyloid degeneration; the picture may then present considerable complexity. Fatty livers may be stained brown or greenish with bile pigment.

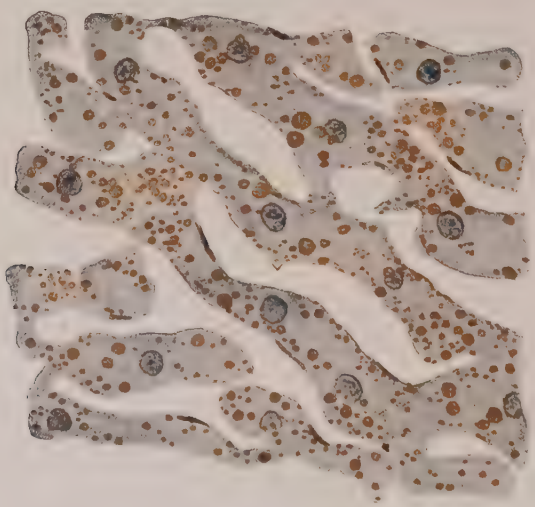


Fig. 533.—Fatty Degeneration of Liver Cells.

Microscopically the liver cells are seen to contain larger and smaller droplets of fat (Fig. 531), and frequently large drops of fat occupy nearly

the entire volume of the cell, so that the protoplasm may be visible only as a narrow, nucleated crescent at one side, or it may disappear altogether (Fig. 532).

Fatty infiltration of the liver may occur as a result of excessive ingestion of oleaginous food; in chronic alcohol, phosphorus, and arsenic poisoning; in certain exhausting diseases accompanied by malnutrition, as in pulmonary phthisis, chronic dysentery, etc.; and under a variety of conditions which we do not understand. It is common in children, especially in acute infectious diseases.[1]

Fatty Degeneration.—In this condition, which in many cases cannot be distinguished morphologically from fatty infiltration, the fat is believed to be formed by a transformation of the protoplasm of the liver cells (page 53). The fat droplets are, for the most part, very small and abundant (Fig. 533), though this is not constant. Fatty degeneration

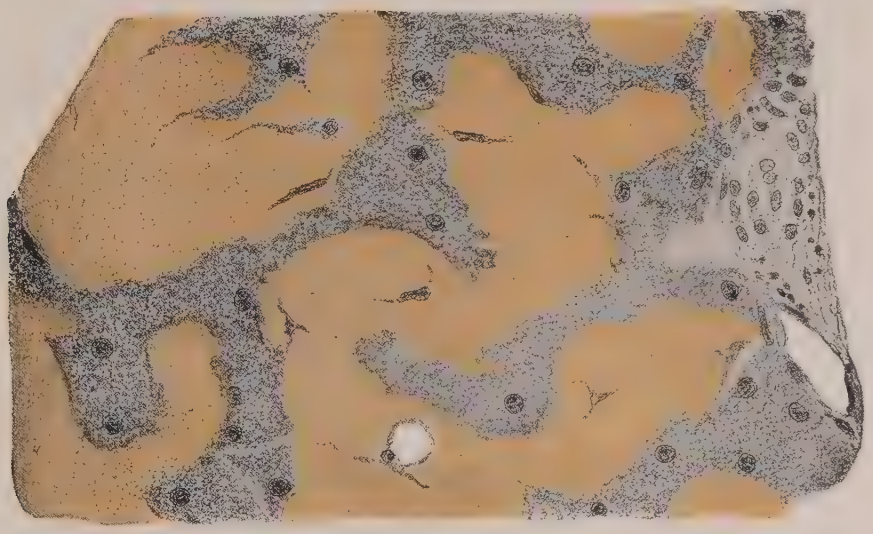


FIG. 534.—AMYLOID DEGENERATION OF LIVER CAPILLARIES.
The capillaries are much enlarged and occluded by the amyloid material; the liver cells between them are atrophied.

of the liver cells frequently follows, and is associated with, cloudy swelling under the varying conditions in which this occurs, or it may appear in profound anemia and in acute phosphorus and arsenic poisoning.[2]

Amyloid Degeneration.—In the liver amyloid degeneration may be general or local; so extensive as to give the organ very characteristic appearances, or so slight as to be unrecognizable without the aid of the microscope. It may be associated with other lesions. When the change is extensive and general, the liver is enlarged, sometimes to more than twice its normal size; the edges are thickened and rounded; the surface

[1] See *Freeman, R. G.*, Arch. Pediat., 1900, xvii, 81.
[2] For a study of localization of fat in the liver, see *McCrae* and *Klotz*, Jour. Exper. Med., 1910, xii, 746.

is smooth; the tissue tough, firm, inelastic, more or less translucent, and of a brownish yellow color. The lobular structure may be more or less indistinct, or it may become very evident by an associated fatty degeneration of the peripheral or central cells of the lobules. The translucency and peculiar appearance of the tissue may be best seen by slicing off a thin section and holding it up to the light. When the lesion is less considerable the liver may be of the usual size, and may feel harder than normal, and here and there a translucent mottling may be evident, or the degeneration may be apparent only on the addition of staining agents. When, as is frequently the case, it is associated with cirrhosis, the liver may be small and nodular, and the appearance of the cut surface may vary, depending upon the character of the cirrhotic change and the presence or absence of fat.

This degeneration usually commences in the walls of the intralobular blood-vessels, causing them to become thickened and translucent (Fig. 534). Their lumen may be nearly or entirely occluded. The liver cells may be squeezed by the thickening of the vessels and may become partially or completely atrophied, or they may be fatty. In advanced stages larger and smaller areas of liver tissue may be almost completely converted into the dense, refractile substance in which here and there flattened liver cells may be seen.

Amyloid degeneration of the liver is usually associated with a similar lesion of other organs.

Glycogen Degeneration.—This may occur in the liver cells in diabetes.

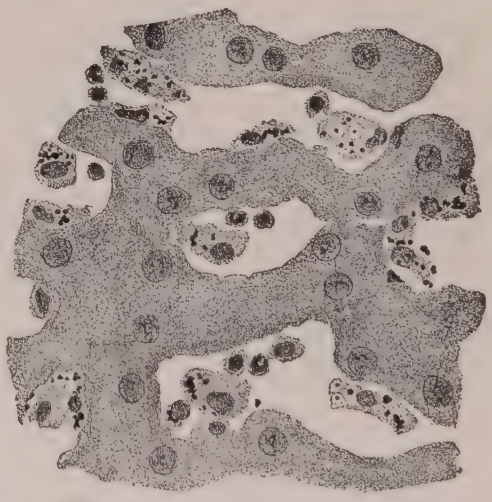


Fig. 535.—Malarial Pigmentation of the Liver.

The pigment is largely in the exfoliated endothelium within the capillaries. Pigmented malarial parasites may be seen in some of the cells.

PIGMENTATION OF THE LIVER.

Pigmentation of the liver cells, from bile and blood derivatives, is to a certain extent normal, but may be greatly increased as a result of atrophy, of localized hemorrhage, and of obstructive jaundice. Hemosiderin is present in large quantities in the liver cells and sinusoidal endothelium in pernicious anemia.[1] Pigmentation of the liver may be marked in hemochromatosis, both hemosiderin and hemofuscin being found (page 69).[2]

As a result of severe malarial poisoning a variable amount of brown, black, or reddish pigment is often found in the blood. This is usually mostly taken up by the leucocytes and deposited in various parts of the

[1] *Rössle*, Verhandl. d. deutsch. path. Gesellsch., 1906, x, 157.

[2] *Rössle*, Zieglers Beitr., 1907, xli, 181 (bibl.); *Opie, E. L.*, Jour. Exper. Med., 1899, iv, 279 (bibl.).

body, chiefly in the liver, spleen, and marrow of the bones. In the liver it is usually found inclosed in the endothelial cells[1] free or in place in the blood-vessels (Fig. 535), but sometimes in the tissue between them. The liver cells frequently contain bile pigment, but usually are free from the melanotic pigment characteristic of this malarial condition. As the result of this accumulation of pigment the liver may have a dark reddish brown, an olive brown, or a black color.

Pigment similar in character to that which occurs in the lungs from the inhalation of coal dust may be found in the connective tissue along the portal vessels. Inhaled pigment particles may pass the lungs and bronchial lymph-nodes, and be deposited in the liver as they are in the spleen and hepatic lymph-nodes. In argyria, the silver granules may be found in the walls of the interlobular veins.

CALCIFICATION.

This lesion of the liver is rare; but it has been seen in eclampsia, chronic nephritis, and tuberculosis. The deposit of lime may be in the vicinity of the arteries or the veins.[2]

INFLAMMATION. (Hepatitis.)

Acute Exudative Hepatitis (Purulent Hepatitis).—Purulent or suppurative inflammation of the liver may be the result of injury; it may be secondary to inflammation of the gall-ducts or of the branches of the portal vein. It may occur as the result of the presence of tumors and parasites, or from propagation of an inflammatory process from without, as in ulcer of the stomach with adhesions to the liver and secondary involvement of the latter. It is not infrequent as a sequence of suppurative appendicitis with pyelophlebitis of the portal vein, and is often directly due to the introduction of bacteria into the organ, through the blood-vessels or gall-ducts or otherwise. Purulent inflammation in the liver almost always results in abscess.

Large abscesses of the liver may be traumatic, but are often due to unknown causes. They are not infrequently associated with dysentery, and may then be due to the conveyance of microorganisms, through the veins, or lymph-channels, or peritoneum, or gall-ducts, from the intestinal ulcers. Such abscesses may be due to the presence of the Amœba coli. They occur most frequently in tropical climates—hence the name *tropical abscess*—but are not very uncommon in the temperate zone. They are usually single, but there may be several of them. They are sometimes so large as to occupy a large part of the lobe; and are most frequent in the right lobe, but may occur in any part of the organ. They tend to enlarge, and as they do so they approach the surface of the liver, where the contents of the abscess may be discharged into the peritoneal cavity. More frequently, however, as they approach the surface a localized adhesive peritonitis ensues, so that the liver becomes bound to adjacent

[1] For a study of the phagocytic powers of the endothelial cells of the blood-vessels of the liver, see *Heinz*, Arch. f. mikros. Anat., 1901, lviii, 576.

[2] See *Brill* and *Libman*, Jour. Exper. Med., 1899, iv, 541; *Rollet, H.*, Frankfurt. Ztschr. f. Path., 1909, iii, 715; and *Ceelen, W.*, Virchows Arch., 1910, cci, 361.

parts, and thus the abscess may open into the pleural cavity, or, owing to a secondary pleurisy with adhesions, into the lung tissue. They may open into the pericardium; externally through the abdominal wall; into the stomach, duodenum, colon, or pelvis of the right kidney; or into the hepatic veins, portal vein, vena cava, or gall-bladder or gall-ducts.

The early stages in the formation of large abscesses of the liver are but little known. It is probable, however, that in many cases they are the result of the confluence of smaller abscesses (Fig. 552). Their contents, usually bad-smelling, may be thick and yellow like ordinary pus, but more commonly are thin, reddish-brown, or greenish in color from admixture with the pus of blood, gall-pigment, and broken-down liver

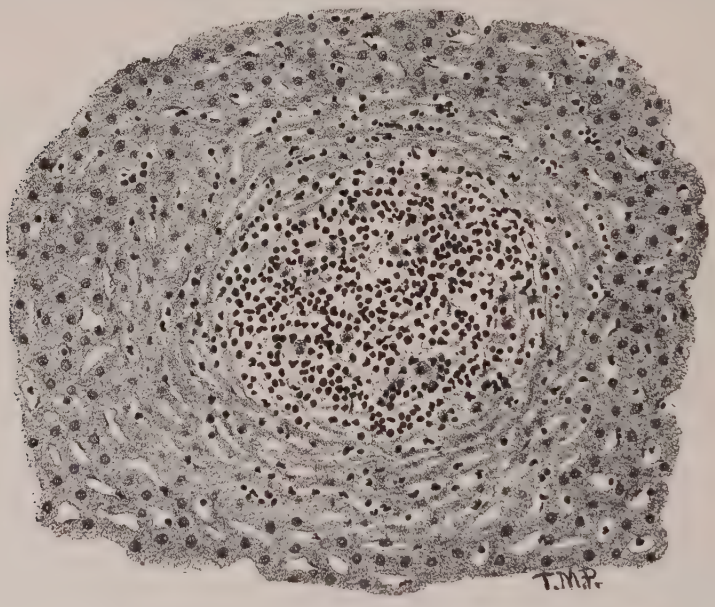


Fig. 536.—Small Abscess in the Liver Containing Bacilli.

tissue. Microscopical examination shows the contents to consist of fluid with pus cells, more or less degenerated blood, degenerated liver cells, fragments of blood-vessels, and pigment granules and crystals. The walls of the abscess are usually ragged, shreds of necrotic liver tissue hanging from the sides. Microscopical examination of the liver tissue near the abscess shows infiltration with pus, flattening of the liver cells from pressure, cloudy swelling, and necrosis of those lying along the cavity.[1]

The amebic abscesses are usually free from bacteria, but are occasionally infected secondarily with organisms of the colon group. Other abscesses may contain the Bacillus coli communis, the Streptococcus pyogenes, or the Staphylococcus pyogenes.

[1] See for a study of tropical abscess of the liver *Howard* and *Hoover*, Am. Jour. Med. Sc., 1897, cxiv, 150, 263 (bibl.).

Not infrequently, however, especially in old abscesses, examination both morphological and cultural fails to reveal the presence of micro-organisms.

After the discharge of the contents of the abscess or without this, if it be not very large, granulation tissue may form in the wall of the cavity and a fibrous capsule be produced. The contents which persist become thickened and often calcareous, and in this condition may remain for a long time. Or the connective-tissue walls may approach one another and join, forming a fibrous cicatrix at the seat of the abscess.

Small multiple metastatic abscesses are not infrequent in pyemia. In these abscesses we can readily study the various stages of formation. Suppurative processes in any part of the body—in the head, upper and lower extremities, etc.—may act as distributing centers for micro-

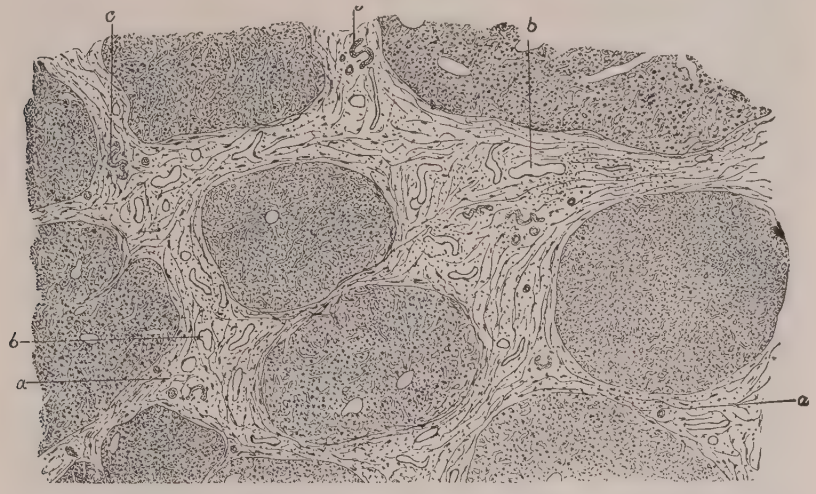


Fig. 537.—Chronic Interstitial Hepatitis—Cirrhosis.
a, New-formed connective tissue; *b*, dilated blood-vessels of the new tissue; *c*, gall-duct.

organisms.[1] Entering the circulation, the bacteria may pass the heart and pulmonary capillaries, with or without inducing lesions in the lungs, and, lodging in the vessels of the liver, induce circumscribed necrosis of the liver tissue (Fig. 61, page 109) and suppurative inflammation. Under these conditions we may find on section of the liver larger and smaller yellowish or grayish spots, the larger of which may be soft and present the usual characters of abscesses. The smaller, which may not be larger than a pin's head, may present the usual consistence of liver tissue with the lobular structure still evident; others may be softer, more yellow, and surrounded by a zone of hyperemic liver tissue. Microscopical examination of the earlier stages often shows the blood-vessels filled with bacteria, scattered and in masses. Around these the liver cells are found in various stages of necrosis; in many the nuclei do not stain and the bodies are very granular, or the entire cell is broken down into a mass

[1] *Kruse* and *Pasquale*, Ztschr. f. Hyg. u. Infectionskrankh., 1894, xvi, 1.

of detritus. About these necrotic islets of liver cells, pus cells collect and often form a zone of dense infiltration (Fig. 62, page 110). Thus, by the increase of pus cells and the necrosis of liver tissue, small abscesses are formed whose contents are intermingled with greater or less numbers of bacteria (Fig. 536), which seem to increase in number as the process goes on. By the confluence of small abscesses larger ones may be formed. Death usually ensues, however, before the abscesses attain a very large size.

Chronic Interstitial Hepatitis (Cirrhosis, Laënnec Type).—Cirrhosis of the liver[1] is a disease characterized by extensive toxic destruction of the liver cells and subsequent connective tissue replacement. There may

Fig. 538.—Chronic Interstitial Hepatitis—Cirrhosis.
On account of the rough surface such livers are sometimes called "hobnail livers." This cut is a photographic reproduction of a cirrhotic liver of a child.

be also as the disease progresses a very considerable restoration of the liver substance by compensatory hyperplasia.

[1] Various names have been applied to the form of cirrhosis described under this head; Portal cirrhosis, Laënnec's cirrhosis, fibrous liver, lacunar cirrhosis, hobnail liver, granular liver. For details of the liver lesions, see *Rolleston*, Diseases of the Liver, 2d ed., London, 1921; *Quincke* and *Hoppe-Seyler*, Krankheiten der Leber, 2d ed., Vienna, 1912; and *Kelly, A. O. J.*, Am. Jour. Med. Sc., 1905, cxx, 951. The earlier bibl. is given by *Paltauf*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1896, i², 301; and *Kretz, R.*, ibid., 1902, viii², 473.

The causes of cirrhosis of the liver are still imperfectly understood.[1] It is commonly a disease of adult life, but exceptionally occurs in children.[2] Congenital cirrhosis with obliteration of the bile ducts has occasionally been noted.[3] Familial occurrence of cirrhosis has been observed in children and is probably related in most instances to progressive lenticular degeneration which is usually accompanied by cirrhosis.[4] In adults, and in some instances in children, the disease seems to be correlated with the continued ingestion of large quantities of strong alcoholic liquor, hence the name "gin drinker's cirrhosis." Acute infectious disease, syphilis, tuberculosis, and malaria have also been regarded as additional

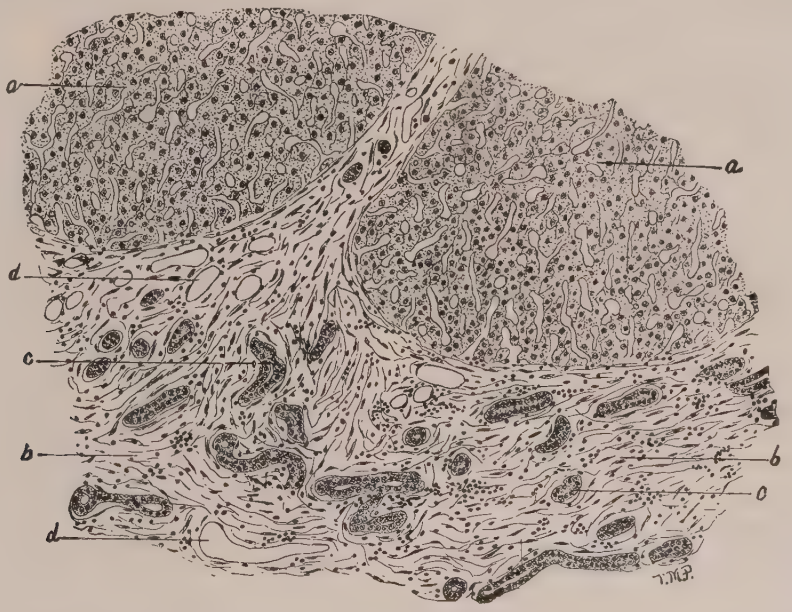


FIG. 539.—CHRONIC INTERSTITIAL HEPATITIS.

Showing a portion of the section shown in Fig. 523, but more highly magnified. *a*, Portions of liver lobules; *b*, new-formed connective tissue; *c*, gall-ducts, apparently new-formed; *d*, blood-vessels in the new tissue.

inciting factors. In all probability there is necessary a combination of toxic agents to produce the lesion. This has been suggested by the results of experimental attempts to produce cirrhosis of the liver in animals.[5] Interstitial lesions have been induced by the injection or inhalation of alcohol but the extent and character of them differ from cirrhosis in man.

[1] For genesis of liver cirrhosis, see *Ribbert*, Deutsch. med. Wchnschr., 1908, xxxiv, 1678, and a very interesting recent review by *Chvostek*. Wien. klin. Woch., 1922, xxxv, 381 and 408.

[2] For a résumé of cirrhosis in childhood see *Morse, J. L.*, Boston Med. and Surg. Jour., 1902, cxlvii, 299; and *Satre*, Progrés méd., 1917, xxxii, 73.

[3] See *Rolleston* and *Hayne*, Brit. Med. Jour., 1901, i, 758 (bibl.).

[4] *Bramwell*, Edinburgh Med. Jour., 1916, xvii, 90; *Tilney* and *Mackenzie*, Neurol. Bull., 1918, i, 243; *Geissmar, J.*, Frankfurter Ztschr. f. Path., 1916, xviii, 305.

[5] *Grover, A. L.*, Jour. Am. Med. Assn., 1913, lxi, 458 (résumé and bibl.); *Fischler*, Deutsch. Arch. f. klin. Med., 1908, xciii, 427. An interesting type of cirrhosis is that produced in cattle by the eating of the rag-wort Senecio jacoboea, and related species. See *Cushny*, Jour. Pharmacol. and Exper. Therap., 1910, ii, 531.

The repeated administration of chloroform to dogs by the stomach so as to cause continuous destructive lesions of the liver cells has, however, produced changes fairly comparable with those noted in man.[1]

If injections of cultures of Bacillus coli are associated with the administration of chloroform, lesions may be induced still more nearly resembling those of advanced cirrhosis with the active new formation of gall ducts. Chronic protein intoxication, produced by the injection of moderate amounts of protein in sensitized animals has been shown also to produce lesions of the liver resembling those of cirrhosis.[2] It is therefore probable that the complete picture is due to alcoholism, plus toxic materials absorbed from the intestinal tract, either through lesions induced by the alcohol, or in the direct course of absorption of food products acting in combination with the alcohol. It may be also that the type of alcoholic drink used or the presence of other alcohols or aldehydes in the fluid has some influence on the production of the disease, the general opinion being that the consumption of gin is especially apt to lead to cirrhosis. Excessive beer drinking may induce cirrhosis but more frequently causes extensive fatty degeneration.

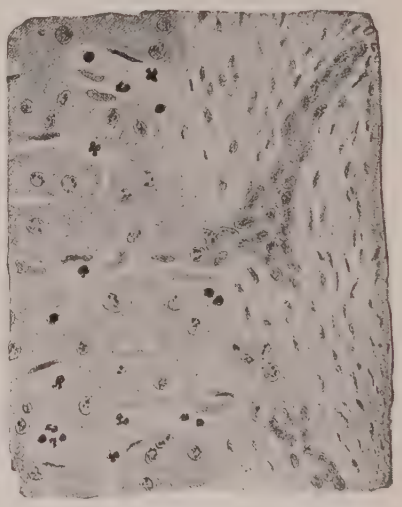


FIG. 540.—NEW-FORMED GALL-DUCTS IN CIRRHOSIS.

The section shows the projection into the new connective tissue from the rows of old liver cells, of cell masses resembling gall-duct epithelium. This may be interpreted as an example of reversion of the differentiated liver cells to a simpler type.

The various appearances which cirrhotic livers present to the naked eye depend largely upon the nature, amount and distribution of the new formed connective tissue, and upon the secondary changes in the liver. As a rule, the loss in volume of the organ is very considerable because the amount of connective tissue present as a replacement fibrosis is rarely in any way equivalent to the total volume of liver substance lost. The organ is therefore almost always smaller than normal. The surface may be very rough and uneven from the projection of smaller and larger, irregularly shaped, nodules of liver tissue, between which are depressed, contracted bands of new formed connective tissue. On the other hand, the surface of the liver may be smooth, when the new connective tissue bands are small, even if the liver is little contracted, or when the lesion is early. Again, the liver may be greatly distorted and misshapen by the atrophy of the parenchyma and the contraction of large and irregular

[1] *Opie, E.*, Jour. Exper. Med., 1910, xii, 367; and *Fraser, A.*, Am. Jour. Med. Sc., 1916, clii, 202.

[2] For relation of cirrhosis to chronic protein intoxication, see *Longcope*, Tr. Assn. Am. Phys., 1913, xxviii, 427.

bands or masses of new connective tissue. In a cirrhotic liver, the new tissue may not be easily visible to the naked eye, or it may appear as gray irregular streaks or bands, or patches, often sharply outlined against a dark red or brown or yellow or greenish-yellow parenchyma. When, as is often the case, fatty infiltration is associated with atrophic cirrhosis, the liver may not only not be diminished in size, but may be larger than normal, weighing as much as 4,000 grams. The consistence of the small livers is usually very firm, and they cut with a gritty feel. Large livers, on the other hand, while often firmer than normal, may not show an extraordinarily firm consistence. Microscopically the new connective tissue in cirrhosis is in some instances of loose texture and contains many types of wandering cells. In other examples, it may be extremely dense and contains comparatively few cells. It is usually however quite vascular, and contains, a relatively large number of elastic fibrils.[1] Connective tissue is most abundant between the lobular masses of liver parenchyma, but occasionally encroaches more or less upon their periphery. Small gall ducts, some of them at least new formed, are usually present in the connective tissue around the islets of parenchyma. Some of these gall ducts may be continuous with old ducts, or with strands of liver cells. By some it is thought that the picture may be interpreted as a reversion of the liver cell to a simpler type; others believe that it presents the formation of new liver cells from the gall ducts, just as in the case of acute yellow atrophy, where an extensive reparative process goes on with reconstruction of new parenchyma.[2]

The newly formed liver cells are characterized by their large size, pale cytoplasm, and wealth of chromatic material in the nuclei. Branches of the hepatic and portal veins, particularly the latter, often become obliterated by pressure from the new connective tissue or from chronic thickening of the vessel walls, so as to seriously interfere with the functions and nutrition of the liver cells.[3] The branches of the hepatic artery are much less liable to alterations than the others. The central veins also persist longer than other portions of the capillary circulation. The bile ducts also may become obliterated or there may be catarrhal inflammation especially of the larger trunks. The capsule of the liver is usually thickened, either uniformly, or in irregular patches, or its surface may be roughened by larger or smaller papillary projections. The liver is frequently bound to the diaphragm or other adjacent organs by connective tissue adhesions. Obstruction to the portal circulation induced by cirrhosis usually gives rise to a number of secondary lesions; since collateral circulation through the small veins of the ligamentum teres is rarely

[1] For a study of the character of the new connective tissue in cirrhosis, see *Flexner, S.*, Univ., Med. Mag., 1900, xiii, 613.

[2] See *Muir, R.*, Jour. Path. and Bacteriol., 1908, xii, 287; *MacCallum, W. G.*, Jour. Am. Med. Assn., 1904, xliii, 649; and *Kretz, R.*, Wien. klin. Wchnschr., 1900, xiii, 271, and Verhandl. d. deutsch. path. Gesellsch., 1905, viii, 54; also *Naunyn*, ibid., p. 59.

[3] For a study of the increase of portal pressure in portal cirrhosis, see *Herrick, F. C.*, Jour. Exper. Med., 1907, ix, 93. For a study of the lesions of the hepatic veins, see *Hess, A. F.*, Am. Jour. Med. Sc., 1905, cxxx, 986.

established in sufficient degree to afford much relief. The hemorrhoidal, oesophageal, and vesical veins may be greatly enlarged, and also the veins of communication between Glisson's capsule and the diaphragmatic veins. In rare instances a very peculiar dilation of the cutaneous veins above the umbilicus is observed—caput medusæ. The enlarged veins may form a circular network around the umbilicus or a pyramidal tumor beside it, or all the veins in the abdominal wall, from the epigastrium to the inguinal region, are dilated. This condition is thought to be dependent upon the congenital nonclosure and subsequent dilatation of the umbilical vein and its anastomoses with the internal mammary, epigastric and cutaneous veins. Not infrequently a dilatation of the veins of the abdominal wall is seen, which has a different origin. This is produced by the pressure of the ascitic fluid often present in cirrhosis, on the vena cava, and is found not only with ascites from any cause, but also with large abdominal tumors.[1]

The presence of ascites is a common secondary phenomenon in atrophic cirrhosis and is generally attributed to the portal obstruction through chronic peritonitis or cardiac failure may play a part. It usually begins at a fairly early stage of the disease, and is apt to increase inconstantly. It generally precedes edema of the feet, but both may appear at the same time. The fluid is clear or more rarely cloudy, yellow brown or greenish in tone, or reddish. It is sometimes mixed with shreds of fibrin, and more rarely with blood. In exceptional instances ascites is not present and then there will usually be found extensive adhesions between the omentum and the abdominal wall. By this means a sufficient by-pass for the blood is offered from the portal system to the veins of the abdominal wall. The Talma operation, which is sometimes very effective, imitates this condition by suturing the omentum to the parietal peritoneum.[2]

The peritoneum remains normal, or may become very opaque and thick. Lesions of the intestines and other viscera are not uncommon, nor is peritoneal tuberculosis a not infrequent complication. The spleen is enlarged in some 80 per cent. of cases of cirrhosis,[3] sometimes to a very considerable degree. When it is not increased in size this may be due to previous atrophy of the organ, or to great fibrous thickening of its capsule, or possibly to hemorrhages from the stomach or bowels which may occur just before death. The pancreas is usually the seat of a more or less marked interstitial hyperplasia.[4] The stomach and intestines are often secondarily affected by the obstruction to the portal circulation. Profuse gastrointestinal hemorrhage may occur, and sometimes causes sudden death. The mucous membrane is then found pale or congested, or with a hemorrhagic serosa. The hemorrhage not infre-

[1] *Gilbert and Villaret*, Rev. de méd., 1907, xxviii, 305.
[2] *Riesman, D.*, Jour. Am. Med. Assoc. 1921, lxxvi, 288.
[3] *Klopstock*, Virchows Arch., 1907, clxxxvii, 111.
[4] For a study of pancreatic lesions in hepatic cirrhosis, see *Lando*, Ztschr. f. Heilk., Abt. f. path. Anat., 1906, xxvii, 1.

quently results from rupture of esophageal varices which are frequently present, especially in the lower portions of the tube, in a considerable proportion of cases of atrophic cirrhosis.[1] The blood may, in this instance, infiltrate the coats of the stomach and intestines. The mucous membrane of the stomach and the entire length of the intestines is frequently the seat of chronic catarrhal inflammation, and is sometimes intensely and uniformly congested, and coated with mucus. In other cases, both the mucous and muscular coats are pale but very markedly thickened. Cirrhosis of the liver is also not infrequently accompanied by chronic diffuse nephritis. The fever, which is seen in the later stages, is due in some instances at least to an accompanying tuberculosis, though it is probably more often an expression of the cholangitis which may form a part of the disease. Mild jaundice is the rule, but the color of the skin is more dull and muddy than in ordinary obstructive jaundice. The blood shows a cholemia. Anemia is the usual rule, but polycythemia has been observed in a few instances, and regularly occurs as a temporary phenomenon after the removal of large quantities of ascitic fluid.

Hypertrophic Cirrhosis (Hanot Type).—There is a form of chronic interstitial cirrhosis in which the growth of new tissue not only occurs between the lobules, but extends into the lobule between the liver cells (Fig. 541). Under these conditions, in an advanced form of the lesion,

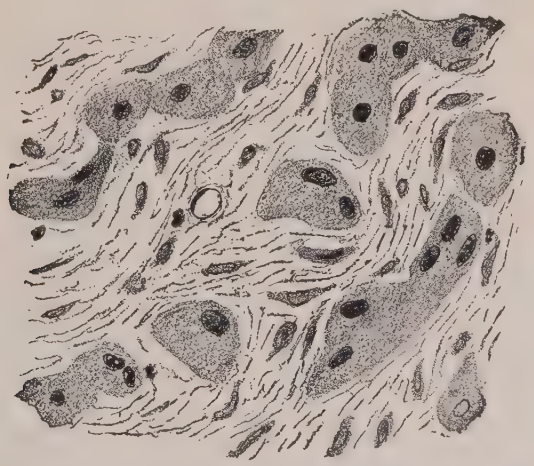


Fig. 541.—Hypertrophic Cirrhosis of the Liver.
Showing formation of connective tissue between the liver cells.

the liver may be greatly enlarged; the surface may be smooth or slightly roughened, and the parenchyma is often deeply bile-stained. Islets of liver tissue are not seen as in the atrophic form. Microscopically there is the formation of a great deal of new connective tissue which

[1] For a critical summary of gastrointestinal hemorrhage in cirrhosis, with bibl., see *Preble*, Am. Jour. Med. Sc., 1900, cxix, 263.

separates individual liver cells or small groups of the latter from each other. The disease is rare and is much more rapidly fatal than the atrophic cirrhosis. Extreme jaundice is frequent.

Biliary Cirrhosis.—Under this title are grouped a series of lesions of the liver which develop from chronic bile stasis, with or without infection.[1] The liver is usually large, smooth, and intensely stained with bile. The cut section is of a deep green color. The amount of connective tissue is not as a rule great, and is chiefly in the region of the bile ducts, though it may spread between the individual lobules, and even separate groups of cells (Fig. 1, Plate XIV A). The microscopic lesions vary. When the lesion is due to bile stasis alone inflammatory effects may be minimal and the chief feature a plugging of the bile capillary with inspissated bile. Even the delicate channels in the liver cells may show a natural injection. Small block concretions of bile pigment may fill the larger bile capillaries (Fig. 2, Plate XIV A). In other types the inflammatory aspects are dominant and the new formed connective tissue about the bile capillaries is filled with wandering cells. Patients with this disease usually die early, but in case they survive atrophy of the liver tissue may be extensive, and the liver become small and hard. Clinically a deep jaundice of the skin is an almost constant symptom, while ascites is moderate or absent. The spleen is not as greatly enlarged as in the atrophic type.

Hemochromatosis.—A very rare type of cirrhosis, usually hypertrophic in form and occurring almost wholly in males is seen in a disease of as yet unknown etiology whose characteristic lesion is a pigmentation of the tissues by hemosiderin and hemofuscin. Fibrosis of many of the organs and often, though not always, a diabetic condition with hyperglycemia and glycosuria accompanies the pigmentation. Hemosiderin is the predominant pigment and may be present in large quantities, the liver containing for example a hundred times its normal amount of iron. It is deposited in the parenchyma cells of the glandular organs (Fig. 1, Plate XIV B), the interstitial cells and tubules of the testis (Fig. 3, Plate XIV B), and in the heart muscle. When the parenchyma cells degenerate from an overload of pigment the latter is set free and is picked up by the cellular phagocytes of the stroma and the vascular endothelium. The hemofuscin is usually contained in the smooth muscle fibers. The endothelial cells of the lymph-nodes also contain much pigment (see Fig. 2, Plate XIV B). The cause of the disease is as yet uncertain, though Mallory thinks it chronic copper poisoning.[2]

Syphilitic Hepatitis.—Chronic interstitial inflammation of the liver

[1] *Ogata, T.*, Zieglers Beitr., 1913, lv, 236.

[2] The recent literature on the subject may be found in *Sprunt*, Arch. Int. Med., 1911, viii, 75; and *Banton, W. B.*, and *Healy, W.*, ibid., 1921, xxvii, 406. See also *Rössle*, Zieglers Beitr., 1907, xli, 181 (bibl.); *Opie, E. L.*, Jour. Exper. Med., 1899, iv, 279 (bibl.). The discussion in the Brit. Med. Jour., 1921, ii, 783–786, contains some interesting viewpoints. For experimental investigation of the problem, see *Rous, P.*, and *Oliver, J.*, Jour. Exper. Med., 1918, xxviii, 629–644; and *Mallory, F. B., Parker, F.* and *Nye, N. N.*, Jour. Med. Res., 1920–21, xlii, 460–490, also Am. J. Path., 1925, i, 117.

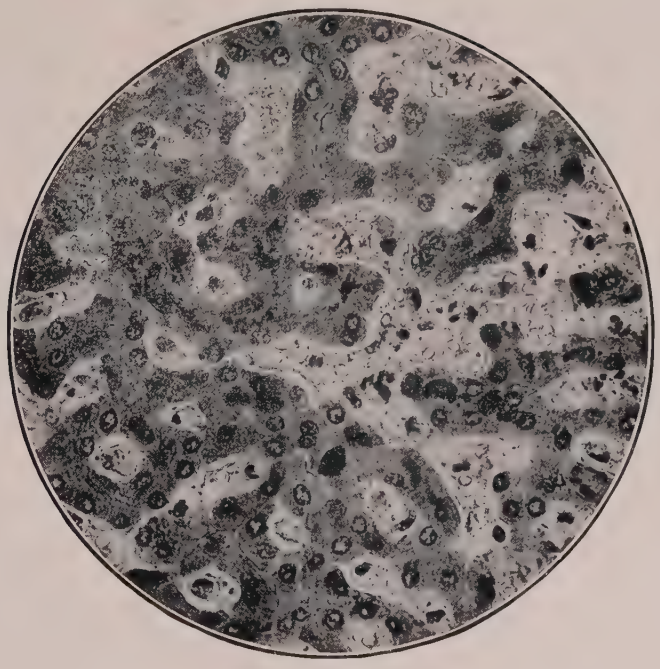


FIG. 1.

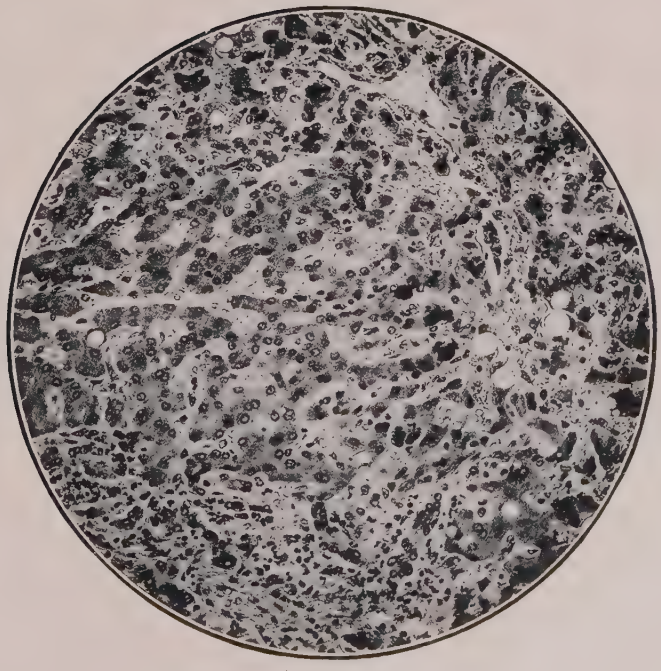


FIG. 2.

Biliary Cirrhosis.

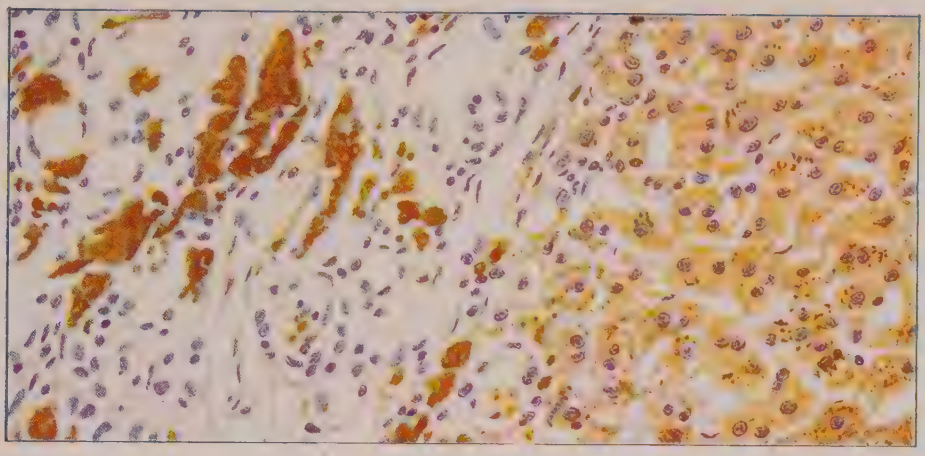


FIG. 1. LIVER.

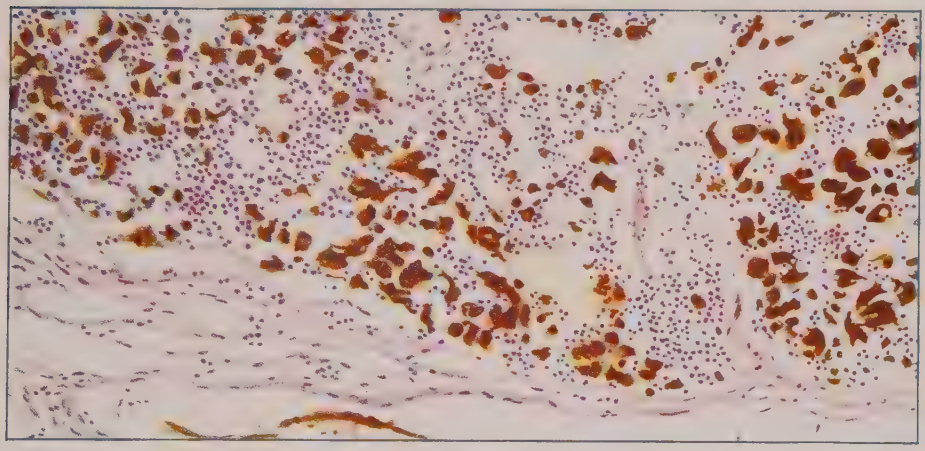


FIG. 2. LYMPH-NODE.

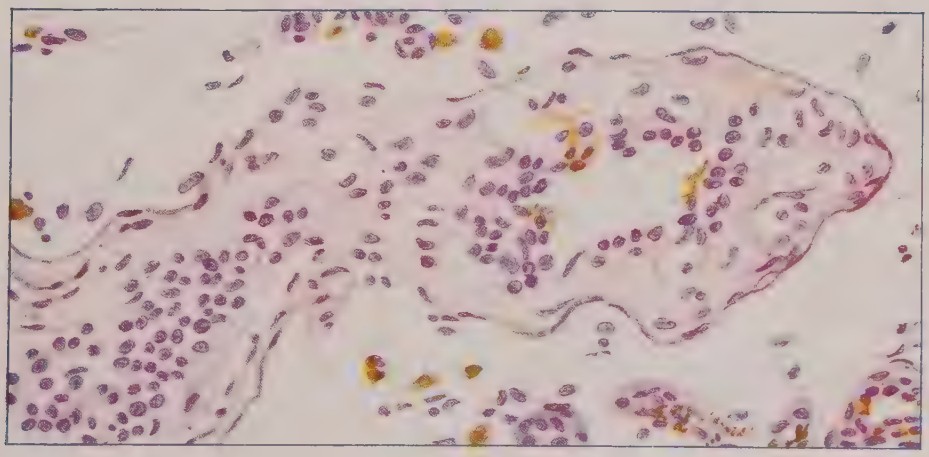


FIG. 3. TESTICLE.

HEMOCHROMATOSIS

very frequently results from syphilitic infection, either congenitally or in the later stages of the acquired form. It may occur in a diffuse manner, new connective tissue being formed either between the lobules or within them between the rows of liver cells. The new tissue may be rich in cells, or dense and firm. This form is frequently seen in children and cannot be distinguished, either macroscopically or microscopically, from similar forms of interstitial hepatitis from other causes.[1]

In other cases, particularly in children, there may be numerous small gummata (so-called *miliary gummata*) (Fig. 170, page 313) scattered through the liver, together with more or less new connective tissue. An extensive formation of giant cells in the liver has been described in connection with congenital syphilis.[2] In adults, gummata are usually larger, varying in size from that of a pea to a hen's egg, and may be surrounded by larger and smaller irregular zones of ordinary connective tissue. In still other cases in adults there are larger and smaller dense, irregular bands or masses of connective tissue running through the liver, drawing in the capsule and often causing great deformity of the organ (Fig. 542). These bands and masses of new tissue may or may not inclose gummata, either large or small. These deforming cicatrices, either with or without gummata, are very characteristic of syphilitic inflammation of the liver.

This, like the simple interstitial inflammation of the liver, may be associated with fatty and waxy degeneration, and with atrophy of the parenchyma from pressure.

Tuberculous Hepatitis.—This lesion, which is usually secondary to tuberculous inflammation in some other part of the body or to acute general miliary tuberculosis, is most frequently characterized by the formation of larger and smaller miliary tubercles, which may be either within or between the liver lobules or in the walls of the bile-ducts. Many of the tubercles are too small to be seen with the naked eye; others may be just visible as grayish points; still others may be from 1 to 3 mm. in diameter, with distinct yellowish-white centers. Microscopical examination shows considerable variation in the structure of the tubercles in different cases, as well as in the same liver. Some of them, usually the smaller ones, consist simply of more or less circumscribed collections of small spheroidal cells, which are not morphologically distinguishable, so far as the form and arrangement of the cells are concerned, from simple inflammatory foci, or from the diffuse masses of lymphatic tissue which occur normally in the liver.

In other forms we find a well-marked reticulum with larger and smaller spheroidal and polyhedral cells, with or without giant cells. In still other forms there is more or less extensive cheesy degeneration

[1] *Symmers, D.*, Internat. Clinics, Ser. 27. vol. i, Philadelphia, 1017.

[2] For a description of congenital liver cirrhosis with giant cells, see *Binder, A.*, Virchows Arch., 1904, clxxvii, 44; also *Lonicer, M.*, Zieglers Beitr., 1906, xxxix, 539 (bibl.).

(Fig. 543). The larger forms are conglomerate, being composed of several tubercle granula joined together to form a single nodular mass. The liver cells at the seat of the tubercle are destroyed, and the interstitial tissue and blood-vessels are either destroyed or merged into the tubercle tissue. In the periphery of the tubercles the liver cells may be in a condition of coagulation necrosis, and the tissue round about may be infiltrated with small spheroidal cells. There is in some cases a new formation of

FIG. 542.—SYPHILITIC HEPATITIS.
The liver is greatly deformed by the contraction of new-formed connective tissue. The ragged surface is due to the tearing away of adhesions to surrounding parts.

gall-ducts or of structures which resemble these and which in transverse sections resemble giant cells. Tubercle bacilli, frequently in small numbers, but often in great abundance, may be found within the tubercles.

Tuberculosis of the liver may be associated with cirrhosis or with waxy or fatty degeneration.

Much more rarely than the above form there are found in the liver more or less numerous scattered tuberculous masses from the size of a pea to that of a walnut or larger, with cheesy centers and usually a new growth of connective tissue in the periphery. These so-called *solitary*

tubercles of the liver may be softened at the centers. Tuberculous inflammation of the gall-ducts may give rise to numerous scattered, cheesy nodules, as large as a pea or larger, which may be softened at the center and stained yellow with bile. Small cavities may thus be formed. This lesion is rare and seems to be more frequent in children than in adults.

Perihepatitis.—*Acute exudative inflammation* of the serous covering of the liver, with the formation of fibrin, may occur as a part of acute general or localized peritonitis, or over the surface of abscesses, tumors, hydatids, etc., of the organ, when these lie near or approach the surface; or it may be secondary to acute pleurisy.

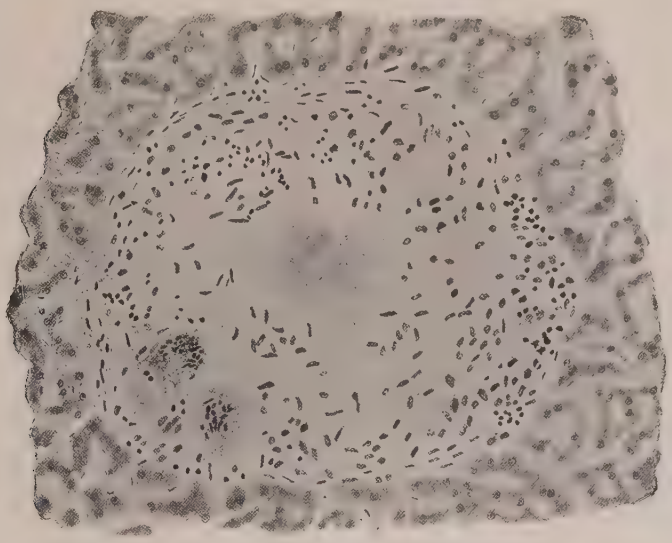


FIG. 543.—A MILIARY TUBERCLE OF THE LIVER.
Showing a cheesy center and giant cells.

Chronic perihepatitis, resulting in the thickening of the capsule of the liver, and the formation of new connective tissue in and beneath it may be secondary to an acute inflammation of the capsule, or it may be chronic from the beginning and associated with chronic pleurisy, chronic peritonitis, and cirrhosis.[2] In this way more or less extensive adhesions of the liver to adjacent structures may be formed; or, by contraction of the new-formed connective tissue, considerable deformity of the liver may be produced. The capsule is sometimes uniformly thickened, sometimes the new tissue occurs in more or less sharply circumscribed patches. The surface is sometimes roughened from little, irregular, projecting masses of connective tissue. Microscopically the new-formed tissue is usually dense and firm, but it may be loose in texture and contain many cells.

[1] See for a study of tuberculous cavities in the liver, *Fletcher, H. M.*, Jour. Path. and Bacteriol., 1900, vi, 147 (bibl.).

[2] Multiple serositis, *Kelly, A. O. J.*, Am. Jour. Med. Sci., 1903, cxxv, 116 (bibl.).

Chronic obliterative pericarditis is often associated with the perihepatitis in which case the cardiac symptoms may dominate the clinical picture.

HYPERPLASIA OF LYMPHATIC TISSUE IN THE LIVER.

In leukemia and in Hodgkin's disease the liver is not infrequently enlarged and soft and sprinkled with small white spots or streaked with narrow whitish irregular bands; or it may be of a diffuse grayish color. Microscopical examination shows that this change is due to an accumulation of lymphocytes, leucocytes, and bone-marrow cells, either along the portal vein, diffusely through the liver tissue, or in small circumscribed masses. The amount of accumulation of these cells varies, but is sometimes so great as seriously to compromise the liver cells. The origin of these cells is not yet definitely known. They may be, and doubtless in part are, brought to the organ through the portal vein; but they may, in part at least, be formed in the liver itself,[1] possibly from the capillary endothelium (Fig. 307, page 545, and Fig. 316, page 563). In pernicious anemia the extensive formation of red cells takes place in the liver, as in embryonic life. In Hodgkin's disease the whitish areas show microscopically the characteristic connective-tissue hyperplasia with large multinucleated cells and often abundant eosinophile leucocytes.

In typhoid fever, smallpox, scarlatina, diphtheria, and measles, small circumscribed masses of spheroidal cells are sometimes found in the liver. These nodules differ in character; some are due to focal necroses, such as occur in various toxemias with a later multiplication of cells or invasion of leucocytes. In some, as in typhoid fever, there is necrosis with proliferation of endothelium (page 277). Finally, some of the small masses of spheroidal cells encountered in the liver in infectious diseases are doubtless hyperplastic lymph-nodules.

TUMORS.

Tumors of the liver may be primary or secondary, the latter being the more common.

Cavernous angioma (*cavernoma, nævus cavernosus*).—These are usually but a few centimeters in diameter, either single or multiple, found most commonly in elderly persons accidentally at autopsy, and are of no practical significance. They may be situated at the surface (Fig. 544) or embedded in the organ, and are of a dark red color; they may be sharply circumscribed by a connective-tissue capsule or merge imperceptibly into the adjacent liver tissue. They are sometimes found in combination with similar growths in other parts of the body, often in the skin.[2] Under the microscope they are found to consist of a congeries of irregular cavities (Fig. 228) filled with blood and frequently communicating freely with one another. The walls of the cavities consist of connective tissue

[1] See, for experimental investigation of this subject and bibl., *Sternberg, C.*, Zieglers Beitr., 1909, xlvi, 586; and *Morris, R. S.*, Bull. Johns Hopkins Hosp., 1907, xviii, 200.

[2] r. *Falkowski*, Zieglers Beitr., 1914, lvii. 385 (bibl.).

often containing small blood-vessels. These growths are believed to be formed by dilatation of the liver sinusoids, perhaps on account of some congenital weakness, with subsequent thickening of their walls and atrophy of the adjacent liver cells. By the organization of clots within the blood cavities these tumors may be partially or entirely converted into masses of dense fibrous tissue.[1]

The cavernoma is regarded by many observers as a hamartoma or developmental error rather than as a true tumor, since there is usually no evidence of actual proliferation in the vessels involved. Yet they may in rare cases invade the surrounding liver, produce symptoms, and actually be the cause of death; so that an occasional example may properly be regarded as a true tumor.[2]

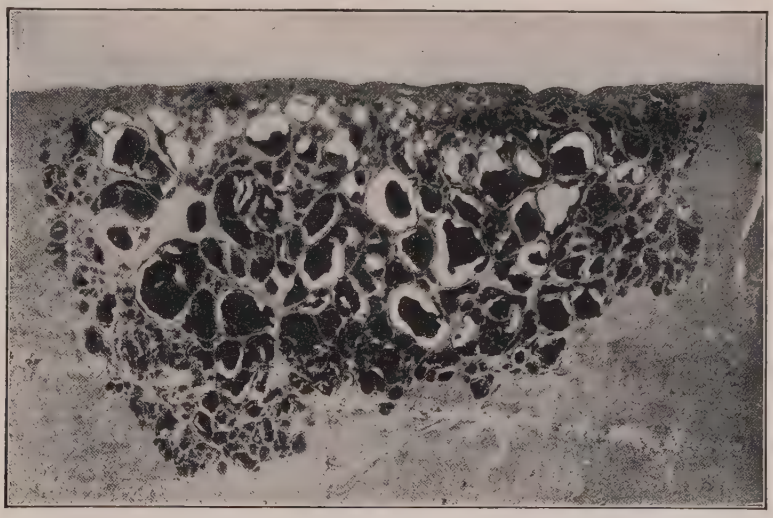


Fig. 544.—Cavernous Angioma of the Liver.

Small **fibromata** and **lipomata** have been described, as also **fibroneuromata** of the sympathetic. Misplaced adrenal remnants are sometimes discovered in the liver,[3] where they may be mistaken for adenomata. Benign and malignant **hypernephromata** may develop from them.[4]

Adenomata[5] of the liver are of not infrequent occurrence. They are sometimes small and circumscribed, sometimes large and multiple. They present two tolerably distinct types of structure. In one, they are of essentially the same structure as normal liver tissue except that the cells are apt to be larger and less uniform in arrangement (Fig. 545). These growths look like little islets of liver tissue, sometimes encapsulated

[1] *Merkel*, Zieglers Beitr., 1904, xxxvi, 574; *Moise, T. S.*, Bull. Johns Hopkins Hosp., 1920, xxxi, 369.

[2] *Roggenbau*, Zieglers Beitr., 1910, xlix, 313 (bibl.).

[3] *Beer*, Ztschr. f. Heilk., Abt. f. path. Anat., 1904, xxv, 381; *Noyes*, Proc. New York Path. Soc., 1899-1900, p. 4.

[4] *Hirschler*, Frankfurt. Ztschr. f. Path., 1812, ix, 343 (bibl.); *White* and *Mair*, Jour. Path. and Bacteriol., 1908, xii, 107 (bibl.); *de Vecchi*, Virchows Arch., 1904, clxxvii, 133 (bibl.).

[5] *Wätzold*, Zieglers Beitr., 1906, xxxix, 456 (bibl.).

and sometimes not, lying in the parenchyma. In the second variety, the cells are less like liver cells, being frequently cylindrical, and are arranged in irregular masses of tubular structure with more or less well defined lumina; metastases may be found in the lungs. These tubular adenomata are in some cases so closely similar to carcinoma as to be scarcely distinguishable from them and seem, indeed, to merge into them.[1]

Carcinoma, which is the most common and important of the hepatic tumors, may be either primary[2] or secondary. Primary carcinomata are derived either from the epithelium of the parenchyma or from that of the gall-ducts, and in some cases are arranged along the larger trunks. The cells are usually polyhedral, sometimes cylindrical, and may be grouped

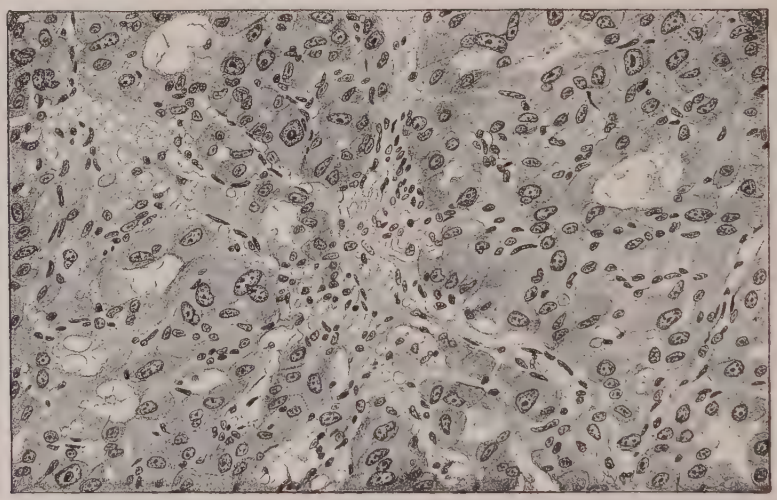


FIG. 545.—ADENOMA OF LIVER.
Showing close resemblance of tumor cells to those of the normal liver

irregularly in alveoli or may form more or less well-defined tubular structures (Fig. 546). Metastasis is relatively uncommon.

Carcinoma of the liver is frequently found in association with cirrhosis,[3] and it should be remembered that it is not a really uncommon growth in children.[4]

Secondary carcinoma, which is by far the more common, is usually due to dissemination of cells from carcinomata of the stomach,[5] intestine, pancreas, or gall-bladder, though it may be the result of metastases from the mamma, esophagus, uterus, or other parts of the body.

[1] For a discussion of adenocarcinoma of the liver, see *Herxheimer*, Centralbl. f. allg. Path., 1902, xiii, 705. For adenocarcinoma with ciliated cells, see *Sokoloff*, Virchows Arch., 1900, clxii, 1 (bibl.). For a discussion of malignant adenoma, see *Blumberg*, Frankfurt. Ztschr. f. Path., 1912, x, 186 (bibl.); *v. Hansemann*, Virchows Arch., 1900, clxi, 453.

[2] *Goldzieher* and *v. Bokay*, Virchows Arch., 1911, cciii, 75 (bibl.); *Herxheimer*, Centralbl. f. allg. Path., 1906, xvii, 724.

[3] *Eggel*, Zieglers Beitr., 1901, xxx, 506 (bibl.); *Winternitz*, Virchows Arch., 1912, ccix, 239 (bibl.).

[4] *Griffith*, Am. Jour. Med. Sc., 1918, clv, 79 (bibl.); *Castle*, Surg., Gynec., and Obst., 1914, xviii, 477 (bibl.).

[5] For a study of retrograde metastasis from the stomach, see *Jacob*, Arb. d. path. anat. Inst. z. Tübingen, 1904–05, p. 121.

The form in which carcinoma of the liver occurs varies greatly. Sometimes the tumors are single, but more often they are multiple (Fig. 547); they may be very large or so small as to be scarcely visible to the naked eye; numerous small nodules are frequently grouped about a larger one. They are sometimes deeply embedded in the liver, at others they project from the surface; and the liver is frequently, and sometimes enormously, enlarged. The nodules are usually whitish or yellowish or pink in color, or bile-stained; they are often the seat of hemorrhages, and may become softened at the center forming cysts. They are sometimes hard, sometimes soft and almost diffluent. Fatty degeneration is frequent and may be recognized by yellowish streaks or patches.

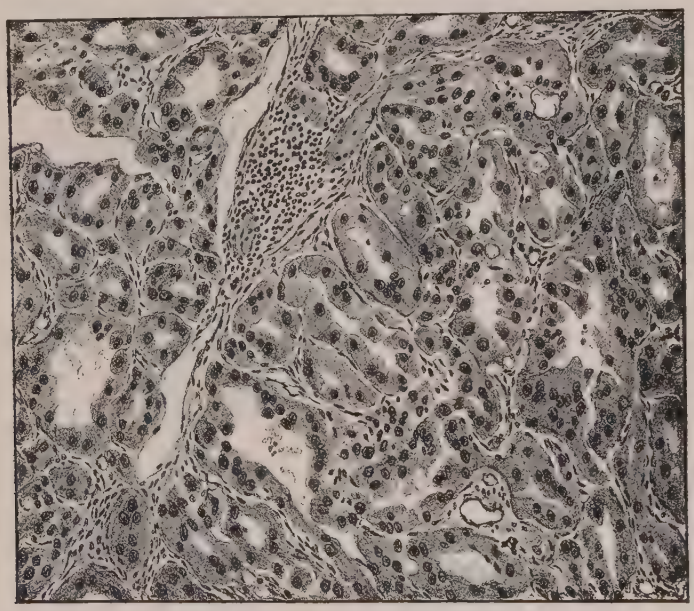


Fig. 546.—Primary Carcinoma of Liver—Tubular Type.

Owing to the degeneration and partial absorption of the central portions of the tumors, nodules on the surface of the liver frequently present a shallow depression at the center. The tumors may be sharply outlined against the adjacent liver tissue or may merge imperceptibly into it. They may be so large or numerous as to occupy the greater part of the enlarged organ and neighboring liver cells may become flattened or atrophic, while pressure upon the portal vein or its branches, or upon the gall-ducts, may seriously interfere with the functions of the organ. On the other hand, large and numerous tumors may be present with no apparent interference with hepatic function.

In some cases, instead of forming separate distinct nodules, the cancerous growth develops in the form of a diffuse infiltration so that the liver is irregularly mottled with white or reddish brown masses and may then somewhat resemble certain forms of chronic interstitial hepatitis; in this type the liver is often greatly enlarged.

A rather atypical diffuse carcinoma has been described under the name *atypical hemorrhagic malignant hepatoma.*[1]

Melanotic carcinomata sometimes occur in the liver, most frequently as secondary tumors. A unique case of primary **chorionepithelioma** of the liver has been described,[2] and referred either to one-sided development of a teratoma[3] (page 1043) or to metastatic chorionic villi, the latter being regarded as more probable.

Sarcoma.—Spindle-cell and **round-cell sarcoma** as well as **angiosarcoma** are among the more frequent types of the rare primary sarcoma of the liver.[4] **Melanosarcoma** has been described.[5]

Spindle-cell, melanotic, and telangiectatic sarcoma may occur in the liver as secondary tumors.[6] Secondary myxomata and chondromata

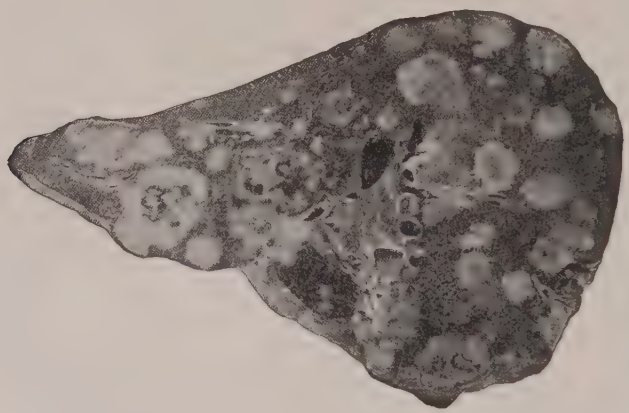


FIG. 547.—SECONDARY CARCINOMA OF THE LIVER.

The section is through the entire organ, showing carcinomatous tumors of various sizes and forms; some are white, some are dark red from hemorrhage. The larger tumor at the left is softening at the center.

have also been recorded, but they are very rare. Cavernous lymphangiomata have been discovered in a few cases.

Cysts.—Cysts,[7] usually of small size, may be formed by dilatation of the bile-ducts. They may be multiple, and contain serum, mucus, and degenerated epithelium. Single cysts, apparently unconnected with the gall-ducts, are occasionally found in the connective tissue of the liver. They may be lined with ciliated epithelium.

The liver is sometimes the seat of multiple cysts, varying from microscopic size to that of a pea or larger. They are sometimes combined with multiple cysts of the kidney and with congenital anomalies in other parts of the body. They may be associated with aberrant bile-ducts, in which they probably originate.[8]

[1] *L' Esperance*, Jour. Med. Research, 1915, N. S. xxvii, 225 (bibl.).
[2] *Fischer*, Frankfurt. Ztschr. f. Path., 1913, xii, 462.
[3] *Albrecht*, Verhandl. d. deutsch. path. Gesellsch., 1902, v, 462.
[4] *Arnold, J.*, Zieglers Beitr., 1890, viii, 123; *Marx*, Centralbl. f. allg. Path., 1904, xv, 433 (bibl.); *Knott*, Surg., Gynec., and Obst., 1908, vii, 328 (bibl.).
[5] *Hetzel*, Ein Fall von Melanosarkom d. Leber, Inaug.-Diss., Erlangen, 1895 (abstr. in Centralbl. f. allg. Path., 1896, vii, 917).
[6] *Hektoen* and *Herrick*, Tr. Assn. Am. Phys., 1898, xiii, 385.
[7] *Dmochowski* and *Janowski*, Zieglers Beitr., 1894, xvi, 102.
[8] *Moschcowitz, E.*, Am. Jour. Med. Sc., 1906, cxxxi, 674.

Teratoma of the liver has been described.[1]

Foamy Liver.—Occasionally the liver is found at the autopsy, even if this be made but a few hours after death, more or less completely riddled with small, irregular-shaped cavities, from the size of a pin's head to that of a pea. These holes are due to the accumulation of gases in the liver, formed by the Bacillus aërogenes capsulatus. This is the so-called "foamy liver" (Fig. 548) and is entirely a post-mortem process.

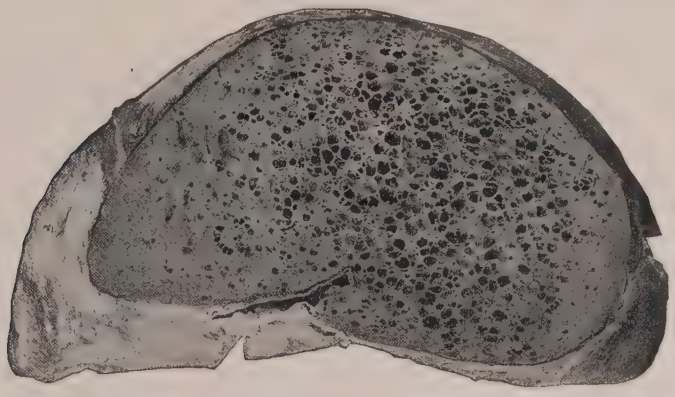


FIG. 548.—"FOAMY LIVER."
The liver is riddled with small holes formed by the accumulation of gas developed by B. aërogenes capsulatus—"gas bacillus."

PARASITES.

Echinococcus.—This parasite is the most common and important of those which occur in the human liver, forming the so-called *hydatids* of the liver which represent one of the developmental stages of the small tapeworm of the dog, Tænia echinococcus (page 151). The cysts in the liver may be very small and multiple, but they may be as large as a man's head or larger. The liver may be greatly increased in size, and the tissue about the cysts atrophied. The liver itself furnishes a connective-tissue capsule, within which is the translucent, lamellated membrane furnished by the parasite. On the inside of this we may find a layer of cells, granular matter, and a vascular and muscular system belonging to the parasite. Projecting from this inner capsule are the brood capsules and heads or scolices of the immature tapeworm. The scolices may become detached from the wall and lie free in the cavity, which is filled with a transparent or turbid fluid. Not infrequently the cysts are sterile, and are then simply filled with clear or turbid fluid; or the embryes may have died and disintegrated, and their detritus, including the hooklets, may be intermingled with the fluid contents of the cysts. The contents of the cysts may be mixed with fat, cholesterin crystals, pus, bile, or blood; or form a grumous mass, in which we may or may not be able to find the hooklets of the scolices or fragments of the lamellated wall. The connective tissue of the walls of the cysts may be greatly thickened, or it may be calcified.

In other countries the lesion is much more common and frequently

[1] *Misick*, Jour. Path. and Bacteriol., 1896, v. 128.

more formidable than in the United States. The cysts reach an enormous size, the veins of the liver may be compressed and filled with thrombi, the bile-ducts compressed and ulcerated. So much of the liver tissue may be replaced by the hydatids that the patient may die from this cause alone. Very frequently there is local peritonitis, and adhesions are formed between the liver and the surrounding parts. In some cases the cysts rupture, and their contents are emptied into the peritoneal cavity, the stomach, the intestines, the pleural cavity, or the lung tissue. Sometimes the cysts perforate the bile-ducts, the vena cava, or some of the branches of the portal or hepatic veins; or the abdominal wall is perforated and a fistula formed between the cavity in the liver and the surface.

Echinococcus multilocularis (page 152), which is apparently an abortive form of the above species, is rare in the United States (Fig. 549).[1]

Fasciola hepatica, Opisthorchis felineus, and **Clonorchis sinensis** may occur in the gall-ducts and gall-bladder. The last-named is found espe-

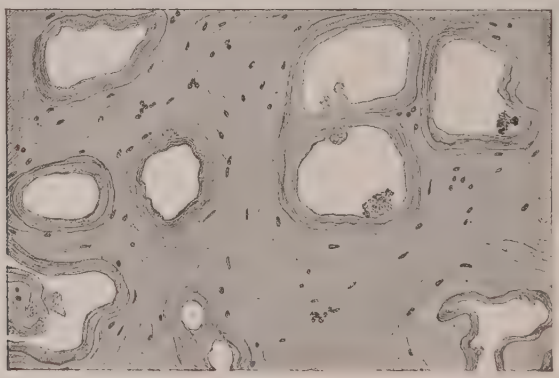


Fig. 549.—Echinococcus Multilocularis of the Liver.

A section of a small portion of the cystic and fibrous growth in the liver. There were no hooklets within the cysts in this case, but the delicately lamellated character of the lining membrane sufficed for a diagnosis.

cially in the East, and has been observed in great numbers in the bodies of Chinamen. **Schistosoma hæmatobium** is very common in Egypt and Abyssinia, occurring in the blood-vessels of the liver. **Schistosoma japonicum** also is found in the liver giving rise to a cirrhotic process (Fig. 86, page 149).

Pentastoma denticulatum is the larval stage of Linguatula rhinaria, a parasite which inhabits the nasal cavity of dogs and some other animals. In the liver of man it usually occurs in the form of small, rounded, calcified cysts. The cysts may contain fat, calcareous matter, and the remains of the dead parasite, among which the hooklets may be found.

Ascaris lumbricoides sometimes finds its way from the intestines into the bile-ducts. It may cause no disturbance here, but in some cases the worms have been present in large numbers and caused occlusion, dilata-

[1] See *Oertel*, Yale Med. Jour., 1899, v, 233; consult also *Posselt, A.*, München. med. Wchnschr., 1906, liii, 537, 605 (bibl.).

tion, and ulceration of the biliary passages, and have led to the formation of abscess of the liver.

Coccidium oviforme, a very common parasite in the rabbit's liver, has been found a few times in the liver of man.

LESIONS OF THE BILIARY PASSAGES AND THE GALL-BLADDER.

The function of the gall-bladder as a receptacle is partially explained by its anatomical structure, the mucosa being folded so as to offer as large a surface as possible for concentration of the bile by removal of water from the dilute fluid excreted by the liver, a fairly extensive lymphatic and vascular system, and a rather limited muscular coat. The purpose of this coat seems to be to keep the contents mixed and to expel bile when needed. It has been shown experimentally that when an animal is in the fasting state, the pressure is low, rarely more than 100 mm. of water, and that this increases after the ingestion of food. Rhythmic contractions of the muscularis cause moderate changes in this pressure. As the secretion of the bile is more or less continuous, and under normal conditions none of this fluid is discharged into the duodenum except during digestion, the bladder functionates as a storage cavity for the fluid. The secretion of the liver is also more active during digestion and the excess is stored till needed for digestion. In other words, the gall-bladder is a part of the mechanism whereby the secretory activity of the liver is correlated with that of the gastrointestinal tract. Practically all of the bile secreted by the liver in a fasting condition is stored in the gall-bladder. When acid chyme, especially if containing abundant fat, passes the papilla or as can be seen in animals when acid is poured into the duodenum, the gall-bladder contracts and extrudes bile. The contractions which occur

FIG. 550.—SUPPURATIVE INFLAMMATION IN THE GALL-DUCTS—CHOLANGITIS.

have recently been demonstrated in man by the use of iodine-containing dyes which, when injected into the blood stream, are secreted by the liver and enter the bladder.[1] Nevertheless, it is obvious that while the gall-bladder has important functions, it is apparently possible for it to be removed by surgical operation and yet the patient remain in perfect health. An occasional occurrence of a hydrops of the gall-bladder due to stenosis of the cystic duct without obstruction of the common duct is a case in point. On the other hand, Rous and MacMaster[2] believe that the removal of the normal gall-bladder entails functional disturbances that are none the less significant because the body adjusts itself to them.

Pathological changes occur in the gall-bladder mainly for three reasons, infection, trauma due to stones, and the altered physiological processes such as stasis, hypersecretion and angulation. As a rule the lesions are not complex, due to the simple structure of the organ and the limited blood and lymphatic supply. On the other hand, our lack of knowledge of the function of the viscus has greatly obscured our understanding of the interpretation that is to be placed upon structural changes.

The arterial supply of the gall-bladder is derived from the cystic artery, one of the main branches of this being distributed to each of the anterior and posterior surfaces. The venous return is almost entirely by way of the portal system, the cystic vein carrying most of the blood into the portal, although small branches extend through the bed of the viscus into the liver. The lymphatic drainage is ample in the region of the ampulla and neck but a portion of the fundus, especially the posterior wall, is largely free from the network which elsewhere enmeshes the viscus.

In rare instances the gall-bladder may be almost wholly embedded in the liver substance but usually it hangs fairly freely from the lower surface. The recent employment of substances excreted into the bladder and opaque to x-rays has cast much light on the varying dimensions and position of the gall-bladder and it is much more movable under physiological conditions than has hitherto been supposed.

A mesentery is present to a variable extent in possibly 5 per cent., but a well-developed one in not over 1 per cent. Volvulus may occur in the latter type and results in complete hemorrhagic infarction with edema of the wall and in the initial stages without evidence of infection.

Occasionally the cystic duct may be double, the aberrant channel usually combining with the normal near the common duct. If the condition is overlooked ligature of the most prominent one and removal of the gall-bladder may lead to serious leakage of bile from the abnormal opening.

Infection reaches the gall-bladder chiefly by way of the portal system, the lymphatic channels from the liver or less frequently through the common duct and cystic duct direct. One of the intestinal group of organisms may be found in obviously infected gall-bladders in about a third of the cases. The colon bacillus or the enterococcus group of organisms is almost invariably found. The typhoid bacillus may be present for many

[1] *Graham* and *Cole*, Jour. Am. Med. Assn., 1924, lxxxii, 613.
[2] *Rous* and *MacMaster*, Jour. Exper. Med., 1918, xxxiv, 75.

years without clinical symptoms, but causes some pathological changes, including the formation of gall-stones. There is no doubt, however, that infection frequently reaches the gall-bladder and becomes active there by way of the general circulation, the teeth, tonsils, or the upper respiratory tract affording portals of entry. Under these conditions a hemolytic streptococcus is the most usual contaminant but in hemorrhagic cases the pneumococcus has been found.

Hypertrophy and Atrophy.—There are also numerous instances of altered gall-bladders with somewhat thickened walls, often fatty deposits beneath the serosa, associated with an enlarged cystic lymph node, and surface adhesions. These are not infected in the sense of presenting bacterial lesions or enabling organisms to be recovered at operation, as they are subacute or chronic processes, never purulent, and only very moderately exudative, even in the most active stages. They are due to contiguous infection in the pancreas, extra- or intra-hepatic ducts or to pyloric or duodenal ulcers. The adhesions to the surface form an important part of the pathology. Organisms may occasionally be demonstrated in the walls by special technics.

Atrophy without obvious infection is seen because of the mechanical processes attributable to calculi which may be present for years without bacterial complications, and also without calculi apparently because of disturbed physiological processes, among these hypersecretion of mucus. Occasional instances of rapid filling with delayed emptying and consequent dilation atrophy of one or more coats, without calculi and without evidence of infection, are seen with the present dye methods which permit visualization of the location, size and movements of the gall-bladder. Acute dilatation is also seen rarely as a complication of typhoid fever, and chronic dilatation due to single or many calculi is not infrequent, but can not be correlated with bacterial processes.

Hyperplastic processes involving the mucosa are much less frequent. Very rarely is actual thickening noted, unless due to productive inflammation. Rarely there is hypertrophy of the epithelial cells at the ampulla or neck, less often of the fundus with hypersecretion of mucus. Under these conditions the penetration of the fibrous and muscular coats by projections of the mucosa, Luschka's ducts, may lead to an erroneous diagnosis of carcinoma (Fig. 551).

The mucosa as a whole very rarely undergoes an adenomatous type of hyperplasia such as is occasionally visible in the Fallopian tubes, but whether this precedes a malignant process is not known. Such processes are not necessarily associated with calculi.

A special clinical variety of chronic degeneration of the mucosa of the gall-bladder has been called the "cholesterol" or "strawberry gall-bladder" (Plate XIV, BII, Fig. 1) because of its appearance.[1] When the viscus is open the mucosa is yellowish or orange, depending upon the amount of bile staining, and is speckled with small yellowish or whitish areas, very minute in size. The wall of the bladder is usually thickened and the organ small in size. The bile content is usually the ordinary

[1] *MacCarty, W. C.*, Ann. Surg., 1910, li, 651; ibid., 1919, lxix, 134.

type of thick yellow bile. The lesion is not very frequent, though in some series it has amounted to 20 per cent. of those removed. The appearance is due to the deposition of cholesterol and lipoid material in the vertices of the tufts of the mucous membrane (Plate XIV, BII, Fig. 2, 3, and 4) and there may also be cholesterol deposits on the surface of the mucous membrane or free in the lumen. The diseased tufts may fall off and become the nuclei for calculi for a considerable proportion of such gall-bladders contain stones (Plate XIV, BII, Fig. 4). More or less evidence of chronic inflammation with edema and fatty infiltration is present in the wall. The epithelium is fairly well preserved. Except for the chronic inflammation present, there is no definite evidence of the

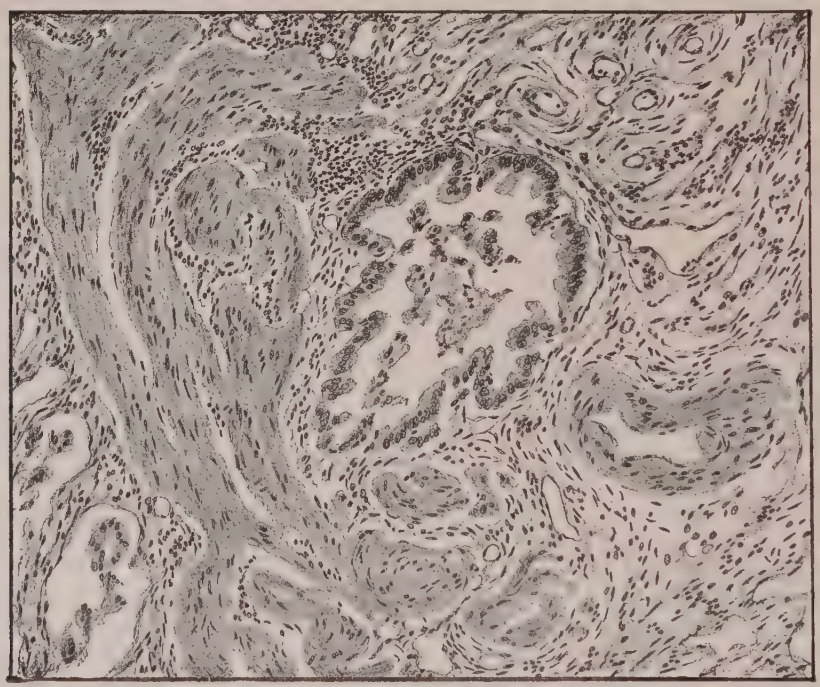


Fig. 551.—Chronic Inflammation of Gall-bladder.
Showing deep penetration down to the subserosa of a Luschka's duct.

causation of this peculiar lesion. Whether it is to be regarded as a definite precursor of cholelithiasis is still under discussion.

Clinically, many of the patients suffer from sharp attacks of pain in the upper right quadrant, with more or less fever and malaise.

Acute Catarrhal Cholecystitis.—The infectious processes include acute catarrhal cholecystitis, a mild form generally not recognizable clinically, in which edema and congestion are prominent and except for degeneration of the lining epithelium, and abundant mucus, may be the only change. Owing to the swelling of the mucous membrane the ducts may become occluded and jaundice ensue, but such occlusion may not be obvious after death. In fact, many of the so-called cases of catarrhal

FIG. 1. Gross specimen showing cholesterol and lipoid flakes on mucous membrane.

FIG. 2. Early stage with foam cells containing lipoid.

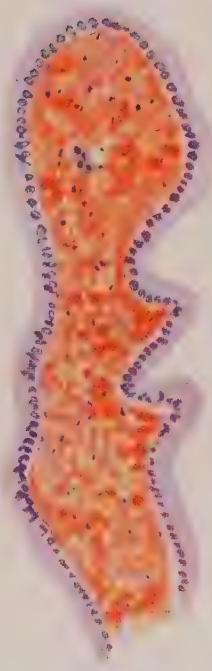


FIG. 3. Later stage, epithelium still intact. Scharlach red stain.

FIG. 4. Degeneration of tuft with escape of lipoid material. Scharlach red stain.

jaundice are in reality light toxic or transient infectious lesions of the liver cells which prevent the excretion of bile into the ducts and in consequence permit its reabsorption into the blood current.[1] In many cases of acute catarrhal inflammation of the gall ducts, the B. coli or typhosus or paratyphosus are found. Rarer infections are with the Friedländer bacillus, pyocyaneus, proteus, influenzæ, and the anaerobic type of gas-forming organisms.

Suppurative and Membranous Inflammation of the Bile-ducts (Cholangitis) and Gall-bladder (Cholecystitis).—The more active and definitely infected gall-bladders are the acute suppurative, subacute purulent, pseudomembranous and ulcerative. Rarely true gangrene occurs, as most of the attacks are mild and a considerable productive inflammation with thickening generally accompanies all the acute and subacute processes. If perforation occurs it is generally high up on the fundus or in the ampulla. These processes correspond to the same types of inflammation elsewhere, but are characterized by early erosion of epithelium and predominant thickening by new fibrous tissue, diffuse lipoid infiltration, new vessels and many endothelial cells. The productive inflammation results usually in a deposit of new tissue outside the muscle coat. Glands are also likely to be partially buried in the subserous coat, sometimes containing precipitated bile pigment and cholesterol or even embedded calculi. Diverticula are acquired in this manner. Ulcerations may persist for years, the wall being converted into a tough hyaline membrane with practically no nucleated cells nor vessels, and the lumen generally filled with calculi.

Suppurative inflammation may lead to perforations of the ducts or bladder, with escape of bile and peritonitis; or to fistulous openings between the gall-bladder and the duodenum, colon, and stomach, or through the abdominal wall; or the inflammation may extend to the liver tissue and produce abscesses. Under the latter conditions there may be a series of small abscesses ranged along the walls of the suppurating gall-ducts (Fig. 552). In more advanced stages the abscesses may become large and communicate with one another, so that a considerable portion of the liver may be occupied by a series of communicating cavities with ragged walls, containing pus and detritus of liver tissue more or less tinged with bile.

Such abscesses may become more or less completely inclosed by connective-tissue walls. The portal vein may also become inflamed, and perforations may be formed between it and the bile-ducts. The excitants of these inflammatory processes in the gall-ducts and gall-bladder are probably usually bacteria. Those which have been most frequently found are the "pyogenic cocci,"[2] the colon and typhoid bacilli, and the pneumococcus. It should be borne in mind that post-mortem invasion of the gall-bladder and passages by bacteria may take place early.

[1] *Heyd, C. G.*, Surg., Gynec. and Obst., 1924, xxxix, 66; *Martin, W.*, Annals of Surg., 1927, lxxxv, 535, (bibl.).

[2] For infections consult *Cushing*, Bull. Johns Hopkins Hosp., 1899, x, 166 (bibl.); and *Posselt, A.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1915, xvii^2, 719 and 1919, xix^1, 351.

Tuberculosis of the gall-bladder occurs in two forms: 1, in conjunction with calculus cholecystitis as a secondary infection in an already diseased bladder; and, 2, as an active ulcerating lesion of the mucosa of the bladder without much thickening. In connection with this form there is usually an accompanying tuberculosis of the bile-ducts. Both forms are merely special localizations of a general tuberculosis existing in the body.[1]

Constriction and Occlusion of the Bile-ducts.—This may be produced by inflammation of the ducts themselves, by new growths in their walls, by calculi or parasites in their lumina, by changes in the hepatic tissue in chronic and acute hepatitis, by aneurysms, or by pressure on the duct from without, as by tumors in the head of the pancreas, etc.

FIG. 552.—SUPPURATIVE INFLAMMATION OF THE GALL-DUCTS IN THE LIVER—CHOLANGITIS.
The suppurative foci are almost coalescent in the infected region. This lesion was secondary to suppurative inflammation in the larger gall-passages with the presence of gall-stones.

The obliteration of the smaller bile-ducts produces no marked lesions. When the ductus communis or the hepatic duct is obstructed, the ducts throughout the liver are frequently dilated and the liver tissue is bile-stained (Fig. 554). The liver may undergo atrophy, cirrhotic changes, and the whole body be intensely jaundiced. When the cystic duct is obstructed the gall-bladder is dilated.[2]

Dilatation of the Bile-ducts is usually produced by strictures in the ways just mentioned, or by calculi. When calculi have produced the dilatation this condition may sometimes continue after they have found their way into the intestines. Sometimes, however, there is very marked dilatation of the bile-ducts without evident present or past

[1] *Simmonds, M.*, Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, 332.

[2] For a study of congenital obliteration of bile-ducts, see *Howard* and *Wolbach*, Arch. Int. Med., 1911, viii, 557.

obstruction. The dilatation may affect only the common and hepatic ducts, or it may extend to the smaller ducts in the liver, which are then dilated uniformly or in sacculated forms. They may contain bile, mucus, or calculi. The liver is at first enlarged, but may afterward atrophy. The gall-bladder may be dilated in consequence of obstruction of the common or the cystic duct. In the latter case it may reach an immense size and form a large tumor in the abdominal cavity. The dilatation is generally uniform, the bladder retaining its normal shape; sometimes, however, there are diverticula, which are usually produced by calculi. If the obstruction to the hepatic duct is incomplete or movable the gall-bladder may contain bile, and often calculi. If the obstruction is

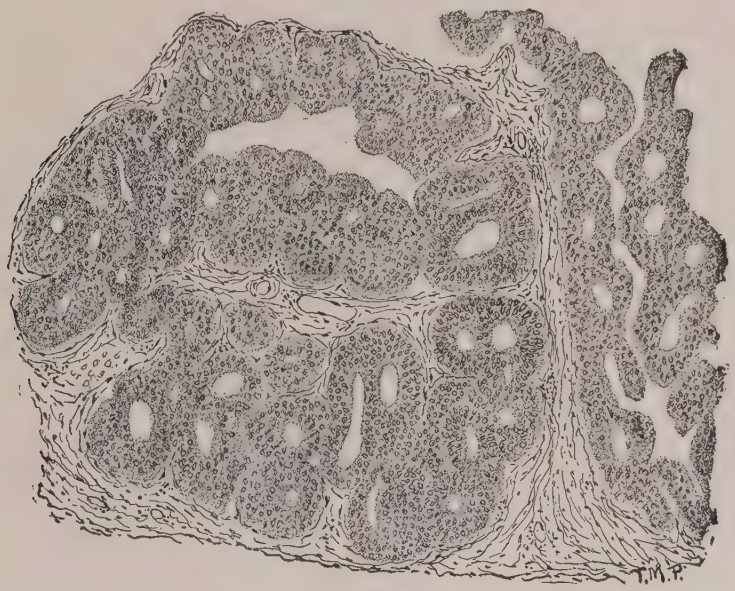


FIG. 553.—ADENOMA OF THE GALL-DUCT.
This section is from a smaller tumor growing within one of the gall-ducts in the liver.

intermittent the contained fluid may gradually lose its biliary character and become a serous or mucous fluid of a light yellow color—*hydrops cystidis felleæ* (Fig. 555). The wall is thick and trabeculated, the tufts are flattened, the epithelium cuboidal, the glands of the submucosa proliferate. The muscular coat is hypertrophied and all layers of the wall inflamed. If the obstruction is due to a calculus, this may pass into the intestine and the gall-bladder be suddenly emptied. Complete obstruction of the cystic duct causes atrophy.

Perforation of the Gall-bladder.—A severe blow over the region of the gall-bladder may cause rupture of that organ. If the abdomen is opened shortly after a perforation has occurred and bile has escaped into the peritoneal cavity, a chemical variety of peritonitis may be found. The lesion rarely remains in this stage, however, for bacterial invasion through

the damaged gut wall is usually prompt and the irritative lesions produced by the biliary fluid are replaced by the more complicated processes accompanying bacterial infections. A more usual cause of perforation is, however, the injury to the walls of the viscus produced by the pressure of gall-stones during the contraction of the bladder while emptying. Ulceration is thus commonly produced and, aided by infection, the wall is ulti-

Fig. 554.—Bile Staining of Liver from Obstructive Jaundice Following Occlusion of Common Duct by a Carcinoma of That Structure.

mately perforated. Interrupted phases of this process are not infrequently met with in routine autopsies without antecedent history of any symptoms referable to the gall-bladder. Under these conditions adhesions may exist between the gall-bladder, stomach, duodenum, transverse colon or even the urinary bladder. The gall-bladder may be free of stones, in which case they have presumably escaped through a stoma which has closed later or stones may still be present. In rare instances the stoma may persist giving rise to an internal biliary fistula.

TUMORS OF THE GALL-BLADDER AND LARGER GALL-DUCTS.

Small **fibromata** have been described in the gall-bladder and in the common duct, but they are very rare. **Adenoma** (Fig. 553) and **papilloma**[1] of the gall-ducts are of occasional occurrence.[2]

The most common tumor, however, is the **carcinoma,**[3] which may be either primary or secondary, and presents the usual structural variations.

FIG. 555.—HYDROPS OF GALL-BLADDER DUE TO BALL-VALVE ACTION OF SMALL STONE IN CYSTIC DUCT WALLS SHOW NO BILE STAIN.

The cells may be cylindrical or polyhedral or present the characteristics of gelatinous cancer,[4] while keratinizing carcinomata and epitheliomata have been described,[5] though they are rare.

[1] *Schoenlank*, Frankfurt. Ztschr. f. Path., 1915, xvi, 293 (bibl.).

[2] For a discussion of diseases of the gall-bladder, including tumors, see *Konjetzny*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1910, xiv[2] 712 (bibl.).

[3] *Sherrill*, Ann. Surg., 1906, xliv, 866 (bibl.).

[4] *Treutlein*, Centralbl. f. allg. Path., 1901, xii, 825 (bibl.).

[5] *Herxheimer*, Zieglers Beitr., 1907, xli, 348 (bibl); *Lubarsch*, Verhandl. d. deutsch. path. Gesellsch., 1906, x, 198, 208; *Nicholson*, Jour. Path. and Bacteriol., 1909, xiii, 41 (bibl.); *Simmonds*, Centralbl. f. allg. Path., 1911, xxii, 577 (bibl.).

Complex tumors of various types are very rare.[1]

Primary carcinoma of the gall-bladder forms about five per cent. of all carcinomata.[2] The disease occurs rather late in life; almost always after forty, and the frequency increases with increasing age. Very rarely cancer has been found in children. In different series the ratio has been found to be three to five times as frequent in women as in men. The most frequent types are a papillary and a diffuse infiltrative. The papillary type grows into the bladder and forms a large bulky mass, filling the organ. Usually adhesions to the liver take place fairly early. Gall-stones may be found embedded in the center of the mass. The infiltrating type involves the wall of the organ, thickens it, with ultimate shrinkage from sclerosis. The liver and nearby organs and the peritoneum are invaded early. A very much less frequent form is the gelatinous, which usually fills the cavity of the gall-bladder and in women frequently involves the ovaries by extension, giving rise to one type of the so-called Krukenberg bilateral ovarian carcinoma.

In about half of the cases of carcinoma of either type the liver is involved by direct extension at the time the symptoms call attention to the disease. Other types of metastasis are occasionally seen, including that to the supraclavicular nodes, the enlargement of which is usually considered to be diagnostic of carcinoma of the intestinal tract. The disease may be accompanied by suppurative processes in the gall-bladder or liver, thrombosis of the portal vein and peritonitis. Microscopically the carcinomata resemble those of the gastrointestinal tract, the glandular form being most frequent. Occasionally the primary tumor is very small, with large metastatic nodules in the liver or other organs and occasionally in the peritoneum. Metastases from carcinoma elsewhere rarely occur in the gall-bladder, though the organ is not infrequently involved by extension from secondary growths of the stomach and pancreas. An interesting feature of this neoplasm is the frequency with which it is associated with calculi. In fact, it forms one of the most striking examples of the effect of chronic irritation in the production of cancer. It is estimated that five per cent. of all those carrying gall-stones over the age of forty ultimately develop cancer of that viscus. As women more frequently have gall-stones than men gall-bladder carcinoma is more frequent in the female. Marchand[3] found that eighty per cent. of the cases of carcinoma showed gall-stones, seventy-six per cent. being women and twenty-four men. The same proportion has been noted in other series. It has been pointed out, also, that only in the case of cholesterin calculi can it be assumed that the calculi antedated the neoplasm.[4] This belief in the correlation between the presence of stones and the appearance of cancer has received interesting confirmation by Leitch[5] by the experimental production of cancer of the gall-bladder in the guinea pig.

[1] *Simmonds, M.*, Centralbl. f. allg. Path., 1911, xxii, 577.

[2] Very complete surveys are in *Rolleston*, Diseases of Liver, Gall-bladder and Bile Ducts, London, 1912, and *Konjetzny*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1910, xiv², 712 (bibl.).

[3] *Marchand*, Wien. klin. Wchnschr., 1921, xxxiv, 606; *Lentze*, Beitr. z. klin. Chir., 1926, cxxxvii, 38; *Latzin*, Arch. f. klin. Chir., 1926, cxxxix, 525.

[4] *Aschoff* and *Bacmeister*, Die Cholelithiasis, Jena, 1909.

[5] *Leitch, A.*, Brit. Med. Jour., 1924, II, 451.

Sarcoma of the gall-bladder, also, is rare.[1]

BILIARY CALCULI. (Cholelithiasis.)

These bodies are of common occurrence. They are found usually in the gall-bladder, sometimes in the hepatic, cystic, and common ducts; less frequently in the small ducts of the liver. In the gall-bladder from 1 to 7,800 calculi have been counted. They vary in size from that of a pin's head to that of a hen's egg, or they may be larger. Single gall-stones are usually spheroidal or ovoidal; when multiple they are usually flattened at the sides or faceted (Fig. 556).

They may be composed:[2]

1. Principally of *cholesterin*, and may be of pure white color, or tinged with various shades of yellow or brown by bile pigment. The fractured surface shows a radiating crystalline structure.

2. Of *cholesterin*, *bile pigment*, and salts of *calcium* and *magnesium*. These are usually dark colored, brown, reddish black, or green, and may

FIG. 556.—BILIARY CALCULI.
The smaller calculi show the faceted character; the larger, cut across, show the lamellation.

be spheroidal or faceted, smooth or rough on the surface; the fractured surface is usually radiating crystalline. This is the most common form.

3. Principally of *calcium bilirubinate*. Such calculi are rare, usually small, very dark colored, and not numerous. They occur not only in the gall-bladder but also in the smaller bile-ducts of the liver, where they incite a fatal form of obstructive jaundice. They may also lie in pockets formed of dilated ducts in the wall of the gall-bladder.

4. Of *calcium carbonate*. These are rare, have a nodular surface, and a clear crystalline, not radiating fracture.

Most calculi are formed around a central mass, sometimes called the nucleus, which may consist of cholesterin, bile pigment, mucus, epi-

[1] *Landsteiner*, Wien. klin. Wchnschr., 1904, xvii, 163 (bibl.); *Schoenlank*, Frankfurt. Ztschr. f. Path., 1914, xv, 307 (bibl.).

[2] For a study of the chemical composition of gall-stones, see *Rosenbloom, J.*, Jour. Am. Med. Assn., 1917, lxix, 1765.

thelium, or masses of bacteria, or more rarely of some foreign body. Thus a dead parasite, a needle, or fruit seeds may serve as nuclei. The body of the calculus may be homogeneous, or lamellated, or crystalline.[1] The cause of calculus formation is usually chronic inflammation of the bile passages with changes in the composition of the bile.[2] Hypercholesterinemia, such as is seen in pregnancy, may be a factor.[3] The rôle of microorganisms in the formation of gall-stones has been the subject of significant studies.[4]

Biliary calculi may remain in the gall-bladder and produce no symptoms, or they may pass into the ducts producing biliary colic. When impacted in the cystic duct they may lead to dilatation of the gall-bladder. They may get into the duodenum, large intestine, or peritoneal cavity by ulceration through the walls of the ducts or gall-bladder. Fatal obstruction has been caused by very large calculi entering the lumen of the gut in this fashion. In the hepatic or common ducts they may obstruct the flow of bile and lead to fatal jaundice. The cause of this jaundice has been usually assumed to be purely mechanical with consequent absorption of the bile constituents into the blood, part to be deposited in the tissues and part excreted in the urine. But recent investigation has thrown some doubt on the completeness of this explanation.[5]

This newer view assumes that not only are the so-called toxic or infectious forms of icterus, such as are seen in the course of infectious diseases, due to direct damage of the liver cell so that it cannot carry on its specific activity and eliminate bile pigment and acids as in health, but that also catarrhal and gall-stone jaundice, long thought to be of obstructive type, are similarly caused by liver cell injuries due to the obstruction.

Recent clinical observation has lent color to this view by demonstrating the occurrence of a "dissociated" icterus in the course of certain infections. Thus the liver cell may be incapable of excreting bile pigment and can still excrete bile acids, or the reverse. Even mild injuries to the liver such as follow ether or chloroform narcosis may cause the bile acids to be noticeably increased in the urine without the occurrence of icterus.

Again, the opinion is gaining ground that the liver cell is not the sole source of bile pigment and that possibly the widely distributed cells of that group of tissues called the "reticulo-endothelial system" may be responsible for part at least of the bilirubin of the blood. Some even believe that the Kupffer cells of the liver sinusoids are more important than the hepatic cells in the formation of bile pigment.[6]

[1] On formation of gall-stones, see *Aschoff* and *Bacmeister*, Die Cholelithiasis, Jena, 1909.

[2] *Kretz, R.*, Krehl and Marchand, Handbuch d. allg. Path., Leipzig, 1913, ii, Abt. ii, 493; and *Kelly, A. O. J.*, Am. Jour. Med. Sc., 1906, cxxxii, 446, 744.

[3] *McNee*, Deutsch. med. Wchnschr., 1913, xxxix, 994.

[4] Consult *Mignot*, Arch. gén. de méd., 1898, ii, 129, 263; *Cushing, H.*, Bull. Johns Hopkins Hosp., 1899, x, 166; *Mieczkowski*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1900, vi, 307; and *Rosenow, E. C.*, Jour. Infect. Dis., 1917, xix, 527 (bibl.).

[5] *Brulé, M.*, Recherches sur les Ictères, 3d. edition, Paris, 1922 (bibl.). See, also, review of the subject by *Lepehne* in Ergeb. d. inn. Med., 1921, xx, 221; and *Whipple, G. H.*, Phys. Review, 1922, ii, 440.

[6] *Rich, A. R.*, Bull. Johns Hopkins Hosp., 1925, xxxvi, 233.

CHAPTER IX.

THE URINARY ORGANS.

The Kidneys.

Anatomy.

THE kidney is a paired organ of great anatomical complexity, correlated in its structure with the manifold activities of its component cells. The vascular supply

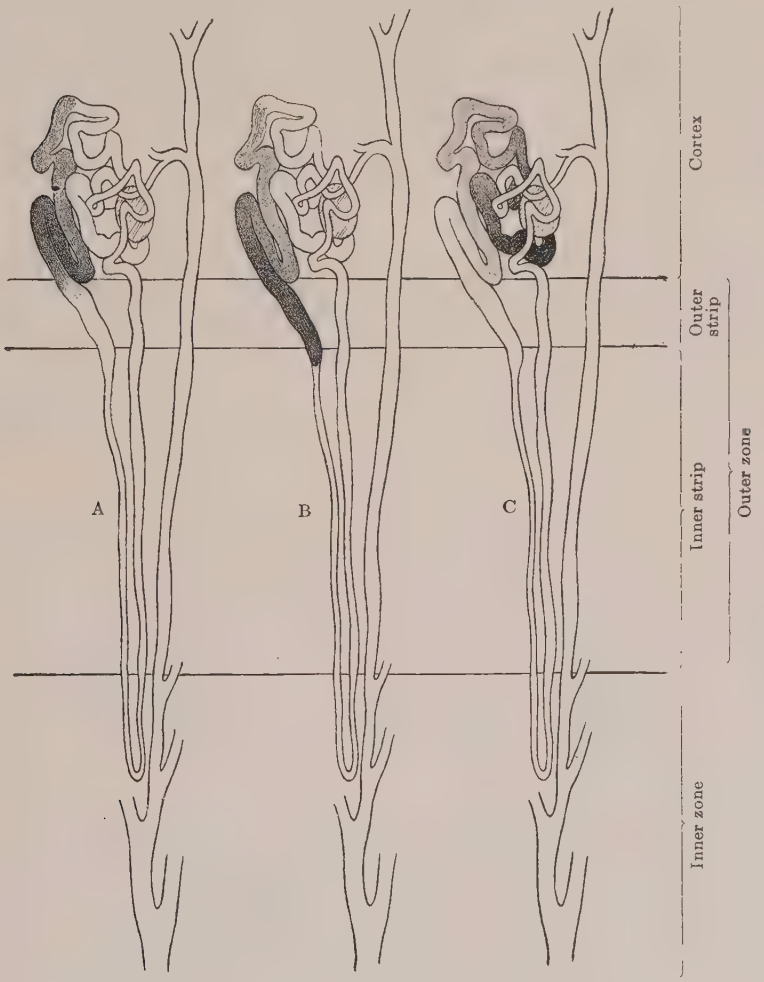


FIG. 557.—SCHEMA OF THE URINARY TUBULES.
Showing the localization of the maximal changes due to *A*, uranium salts, *B*, mercuric chloride, *C*, chrome salts. (*After Suzuki.*)

is so large that the whole of the blood in the body passes through the kidney every few minutes.

The important unit structure is the kidney tubule. This begins as a cup-shaped cavity inclosing a tuft of arterioles covered with flattened cells. On leaving the Malpighian corpuscle the tubule narrows to a neck, then becomes convoluted, forming the proximal convoluted tube (*Hauptstück*), some 14 mm. in length. Differences in impregnation of the lining cells with carmine, and the results of poisoning with metallic salts suggest that there are four different segments of the convoluted tubule considered functionally (Fig. 557). The tubule gradually approaches the nearest medullary ray, still spiral or zigzag in shape, and turns toward the medulla as the descending portion of the loop of Henle, which is narrow, measuring only one third of the diameter of the convoluted tubule, though the lumen is as large as that of the convoluted portion. Near the papilla, while still of small diameter, it turns about, enlarging somewhat, and runs back toward the cortex as the distal or ascending loop of Henle, to touch the glomerulus from which the tubule originally sprang. The length of Henle's loop varies, but the average is about 9 mm. The tube again becomes convoluted on leaving the region of the Malpighian corpuscle to which it had returned. This part is called the second or distal convoluted tubule (*Schaltstück*). This has two portions: (*a*) the intermediary piece, about 0.8 mm. long, which forms the transition between the distal loop of Henle; and (*b*) the true distal convoluted tubule. Its lumen is wide and the lining epithelium is low. The distal convoluted tubule is about 4.5 mm. long; its contour is irregular, the lumen is large and often pouched; and the epithelium is low. It once more narrows into the so-called junctional tubule, and taking a transverse course toward the medullary ray enters one of the straight or collecting tubules which lead to the papilla and the pelvis. The total length of a renal tubule is from 30 to 38 mm., depending upon the situation of the glomerulus.

FIG. 558.—SECTIONS, AT VARIOUS LEVELS, OF THE URINARY TUBULE.
A, Convoluted tubule. *B*, Descending loop of Henle. *C*, Ascending loop. *D*, Intermediary piece. *E*, Collecting tubule.

The epithelium lining the convoluted portion is high and cylindrical. The cell substance is granular and has a rod-like arrangement which terminates on the free surface in a thin layer of rods like short cilia. The descending loop of Henle is lined with very low epithelium which is not granular. The ascending loop, on the contrary, has granular cells and a rod-like structure, but no rod border. The intermediate piece has low epithelium which becomes thicker in the distal convoluted portion. The collecting tubules can be distinguished from the descending loop by their sharply outlined cells.[1]

While the distinction between the cortical and the medullary substances of the kidney is usually made without difficulty in normal organs, there are several smaller divisions of some anatomical importance which are less easily differentiated. The cortical substance, which measures 4.8 mm. in thickness, is conventionally divided into a labyrinthine portion, in which lie the glomeruli surrounded by convoluted tubules, and the medullary rays, where the convoluted tubules pass downward to enter Henle's loop. Recently it has been shown that the medullary portion, which is 18.3 mm. thick, is divided into an outer or boundary zone, measuring 8.2 mm., and an inner or papillary zone, measuring 10.1 mm. The outer zone is again divided by

[1] For further details and bibl., see *Peter*, Bau und Entwicklung der Niere, Jena, 1909; *Suzuki*, Morphologie der Nierensekretion, Jena, 1912; *Schäfer, E. A.*, Text Book of Microscopic Anatomy, Quain's Elements of Anatomy, vol. ii, part 1, London, 1912; *Cushny, A. R.*, The Secretion of Urine, New York, 1917.

a narrow line into an outer and an inner strip. The outer strip is the point of termination of the convoluted tubule, where it enters the descending loop of Henle; it also contains the collecting tubules which are joined by the horizontally running intermediary pieces. The inner strip contains only the descending and ascending loops of Henle and the collecting tubules. The inner zone contains only the clear thin portions of Henle's loop together with the collecting tubules. Transverse sections made at these different levels, therefore, will show different types of tubules (Fig. 558).

The blood after flowing through the glomerulus enters a dense meshwork of capillaries which surround the tubules. The exact relationships between the morphological structures of the tubules and their functional activities is, despite an enormous amount of experimental and clinical research, by no means clear. It seems probable, from the study of dye elimination and the phenomena subsequent to injury of portions of the tubules by poisons, that the salts are filtered through the glomeruli, and many of the colloid materials also, such as albumin and hemoglobin, though only after slight injury. It seems likely that the tubular epithelium has relatively little excretory power, except possibly for a portion of the uric acid and the phosphates; but that the highly diluted filtrate from the glomeruli has its composition altered in its passage down the tubule by selective absorption of certain substances by these cells. It is thought that there is thus removed from the glomerular filtrate 50 per cent. of the water and most of the glucose, while it has been calculated that 99.9 per cent. of the chlorides passing the tufts is turned back into the blood. Amino-acids, also, are returned, and more alkali than acid, the tubular epithelium rejecting the phosphoric acid in the phosphates. Hence, the urine is acid, while the blood from which it comes is faintly alkaline. The capacity of the tubular epithelium to absorb substances may be stimulated or depressed. Thus, phlorhizin interferes with the return of the sugar, hence, the urine after exhibition of this glucoside contains glucose. Uric acid probably is excreted in part through the tubular epithelium, and atophan increases the permeability for this substance without damaging the kidney, as do the salicylates.

Malformations.

Both kidneys may be absent in connection with extensive malformation in fetuses which are not viable.

Absence of one kidney is not uncommon, the left kidney being missing more frequently than the right. The absence of the kidney may be complete, the ureter also being absent; there may be an irregular mass of much atrophied kidney tissue with connective tissue and fat; or there may be only a little mass of connective tissue and fat representing the kidney, and a ureter running down to the bladder. The single kidney which is present is usually much enlarged. It may be in its natural position or displaced downward. When both kidneys are present one of them may be much larger than the other. One kidney may have two pelves or two ureters.

It is not impossible that some of the very much shrunken kidneys found in adult life may be due to prenatal interference with vascular supply or closure of the ureter including atrophy.[1]

A frequent malformation is the so-called *horseshoe kidney*[2] (Figs. 193 and 559). The lower ends of the kidneys are joined together by a commissure, which is composed usually of kidney tissue, but sometimes of connective tissue. The two kidneys may be normal, except for the commissure; or their shape, the arrangement of the vessels and ureters, and the position may be unnatural. The two kidneys may be united throughout so as to look like a single misshapen kidney with two or more pelves and irregular blood-vessels. The united kidneys may both be situated on one side of the vertebral column or in the pelvis. The adrenal glands remain in their normal position in the body even when the kidneys are greatly displaced.

[1] See *Ballowitz*, Virchows Arch., 1895, cxli, 309; *Scheuer*, Ztschr. f. Heilk., 1907, xxviii, 120.

[2] For a study of various types, see *Eisendrath*, *D. N.*, Surg., Gynec., and Obst., 1912, xv, 467.

Double ureters may occur with normal kidneys.[1]

The fetal lobulation of the kidney frequently persists during adult life (Fig. 560).

Fig. 559.—Horseshoe Kidney.

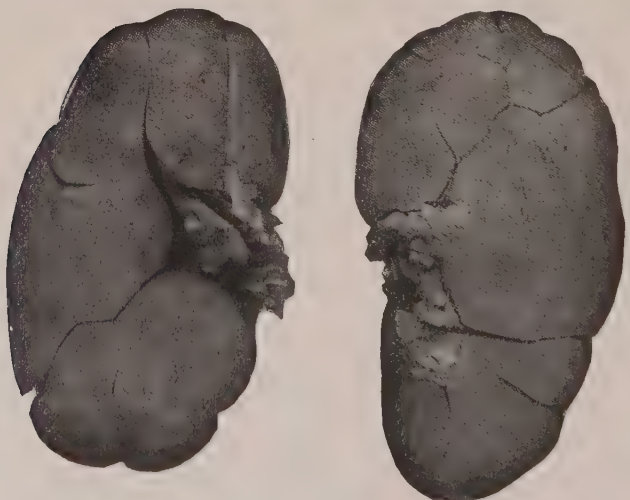


Fig. 560.—Fetal Lobulation of Kidneys in Adult.
The kidneys were of normal size.

Changes in Position.

The kidneys may be placed in an abnormal situation, in which they are either fixed or movable.

[1] *Meyer, R.*, Virchows Arch., 1907, clxxxvii, 408. For a general survey of the subject, see *Huntington, G. S.*, Variations of the genitourinary tract, Harvey lectures, 1906–07, Philadelphia, 1908, p. 222.

The change in position is either lateral or downward. When displaced downward the kidney may be over the sacrum or below this in the cavity of the pelvis. The vessels also have an irregular origin and distribution.[1] The kidney is firmly attached in its abnormal position.

Movable or wandering kidneys are found in adult life, especially in those with general enteroptosis, but also as a result of tight lacing, of overexertion, and of unknown causes. They are very common in females, particularly those who have been pregnant; and the right kidney is most frequently involved. The blood-vessels become lengthened and the attachments of the kidneys longer and looser. Mobility in males is infrequent.

COMPENSATORY HYPERTROPHY OF THE KIDNEY.

In congenital absence of one kidney or in post-embryonal life when one kidney is involved in lesions which seriously interfere with its function, the other organ may increase in functional capacity through an hypertrophy and hyperplasia of its gland cells. A similar alteration may take place in the sound parts of an organ partially compromised by structural lesions.[2] The marks of hypertrophy are not evident in the glomeruli and convoluted tubules. The epithelial cells are larger and increased in number; the tufts of the glomeruli also are enlarged.

REPAIR OF THE KIDNEY.

The tubular tissue of the kidney has but little regenerative power; the glomeruli none at all. A certain amount of regeneration of the tubular epithelium occurs with moderate toxic destruction, especially subsequent to sublimate poisoning, and also after experimental hydronephrosis when the obstruction is relieved. Regeneration of the tubules to a moderate degree may be seen after operative incision into the substance, but most of the reparative material is connective tissue.[3]

ATROPHY.

In old age, the kidney may atrophy, with increase of the fat of the capsule and hilus. The cellular elements and the glomeruli also shrink, and the latter show hyaline changes. The tubular epithelium may be pigmented, and minute calcified cysts may be apparent on section. When the flow of urine from the kidney is suddenly stopped, the kidney may atrophy, with replacement fibrosis, but the glomeruli survive for a long period. If the interruption is intermittent or slow, hydronephrosis results (page 901). Vascular changes leading to diminished blood supply cause atrophy of the kidney (page 867).

DISTURBANCES OF CIRCULATION.

Anemia of the kidney occurs in general anemia: it may be associated with various forms of diffuse nephritis. Local anemia may be due to thrombosis or embolism.

[1] *Anitschkow, N. N.*, Virchows Arch., 1912, ccvii, 213.

[2] For a study of this condition see *Sacerdotti, C.*, Virchows Arch., 1896, cxlvi, 267 (bibl.). Consult also for general consideration of hypertrophy, *Thoma*, Text-book of General Pathology, English translation, London, 1896, vol. i, 448.

[3] *Wood, F. C.*, Process of Repair, Keen's Surgery, Philadelphia, 1906, i, 410.

Acute Hyperemia—Acute Congestion.—This may occur in early phases of an acute inflammatory process or after the ingestion of irritant poisons. The kidneys may be swollen, and the vessels distended, and bloody fluid may exude from the cut surfaces. There may be extravasation of red blood-cells from diapedesis.

Chronic Hyperemia—Chronic Congestion.—This may occur in connection with a similar condition in the other viscera when the circulation is impeded through uncompensated lesions of the heart and lungs, such as chronic endocarditis involving the aortic and mitral valves, cardiac dilatation, aortic aneurysm, emphysema, or large accumulations of fluid in the pleural cavities; or it may be associated with obstruction of the renal vein or inferior vena cava by thrombosis or pressure from tumors, etc. The kidneys in this condition are, when typical, slightly or considerably enlarged, increased in weight, hard, and dark red in color with capsule not adherent and surface smooth. The congestion is most marked in the capillaries of the glomeruli, which are widely dilated, often with thickened walls, in the interlobular veins, the vasa recta, and the stellate veins of the cortical surface.

The epithelium of the convoluted tubules may be swollen; or it may be much flattened so that the lumen of the tubule is enlarged. If the congestion persists, there is hyperplasia of the interstitial tissue of the kidney with degeneration of the epithelium, the formation of casts, atrophy of the tubules, etc. Chronic congestion may lead to chronic diffuse nephritis.[1]

Embolism, Thrombosis, and Infarction.—If the renal artery or one of its branches be plugged by an embolus or thrombus, an anemic infarct of the region is the result. There may be one or several such infarcts which are usually more or less wedge-shaped, the apex directed inward, corresponding to the vascular territory compromised. They are pale or yellowish, and hard, and, as inflammatory reaction sets in, may be surrounded by a red hyperemic zone.[2]

Within the limits of the infarct, necrosis of epithelium or of the entire mass of involved tissue may take place with such subsequent alterations as have been already described on page 40.

The seat of old and healed infarcts may be indicated by small fibrous cicatrices.[3]

Hemorrhagic infarcts in the kidney are rare. Infarcts may become the seat of gangrene when putrefactive bacteria gain access to them; or suppurative inflammation with the formation of abscesses may occur. Embolism of the renal artery may result in necrosis of the entire kidney. Thrombosis of the renal vein may be induced by the pressure of tumors, either on this vessel or on the vena cava; or it may occur in cachectic conditions.

[1] For a study of theories of renal secretion, see *Lamy* and *Mayer*, Jour. de phys. et path. gén., 1906, viii, 660; and *Cushny*, *A. R.*, The Secretion of Urine, New York, 1917.

[2] Studies in infarction: Experimental bland infarction of the kidney and the spleen. *H. J. Karsner* and *J. H. Austin*, J. A. M. A., 1911, lvii, 951.

[3] For a study of the regenerative capacity of the renal epithelium in infarcts, see *Thorel, C.*, Virchows Arch., 1896, cxlvi, 297 (bibl.), and Deutsch. Arch. f. klin. Med., 1903, lxxvii, 29.

DISTURBANCES IN EXCRETION.

Albuminuria.—Albuminous material or serum, with or without hemoglobin, not infrequently passes out of the blood-vessels of the kidneys through the glomerular tufts, and mingles with the excreted substances. It may also be set free by abnormal metabolism or disintegration of the renal epithelium. While this may occasionally occur under conditions which can not be shown to be abnormal, it is common in many diseases of the kidney, and is frequent, without marked kidney lesions, in fevers, infectious diseases, abnormal conditions of the blood, various forms of poisoning, disturbances of the circulation, ingestion of large amounts of native protein, especially egg albumin, etc. Even when kidney disease exists, the excretion of albumin may be very small in amount or may entirely cease so long as the patient is in a recumbent position, becoming large in amount, however, when the erect posture is assumed.

An especial form of albuminuria without the accompaniment of casts or red blood-cells is seen in children, especially those of feeble or anemic constitution. It is perhaps best described as "*postural*" or "*orthostatic albuminuria*," and seems to be due to circulatory irregularities in the kidneys of children who remain long in a strained position. A spinal lordosis is responsible for a certain number of instances, and the erect posture alone may at times bring on the phenomenon.[1]

In albuminuria with pronounced kidney lesions there are usually well-defined alterations in the capillaries of the tufts and in their epithelial investment. There may be thrombi in the capillaries; their walls may be thickened; the flat epithelium covering them may be swollen or fatty; or it may peel off or proliferate. In the kidneys of persons with pronounced albuminuria, albuminous material may be seen as fine or coarse granules within Bowman's capsule or in the lumina of the tubules, after preservation in alcohol or other fixatives which coagulate albumin. Albuminous material in the tubules may form casts (see below), or when the conditions are favorable fibrillar fibrin may be formed.

Hematuria.—The appearance in the urine of blood in considerable quantities may be due to hemophilia, to acute or chronic nephritis, to tumors of the kidney, to renal tuberculosis, or to stone in the pelvis. There is one type of hematuria, however, in which none of these causes can be demonstrated, and to this, because of the lack of a suitable name, the term "*essential hematuria*" has been applied. The disease occurs most frequently in males between the ages of forty and fifty years. The amount of blood passed may be large, and its appearance is usually intermittent, with considerable periods between the attacks. The phenomenon may last for years, and in order to stop the hemorrhage it may be necessary to remove the kidney, though occasionally a cure has been observed after incision of the kidney or even after stripping of the capsule.

The hemorrhage has been ascribed to a variety of lesions. Although

[1] *Jeanneret*, Arch. de méd. d. enfants, 1915, xviii, 461; *Hill, L. W.*, Am. Jour. Dis. Child., 1918, xv, 146 (bibl.); *Langstein*, Pfaundler and Schlossmann, Diseases of Children, English trans., 2d ed., Philadelphia, 1912, iv, 1; and Die Albuminurien älterer Kinder, Leipzig, 1907; and *Jehle*, Ergebn. d. inn. Med. u. Kinderheilk., 1913, p. 808.

the kidneys are, as a rule, not especially movable, it has been thought that a slight kinking of the renal vein, with the incident chronic congestion, might cause the bleeding. Again, as there is often a fairly extensive arteriosclerosis of the kidney vessels, or erosions in the pelvic mucous membrane, or a papillitis or varicosity of the veins of the renal papillæ, these lesions have been considered as explaining the hemorrhage; but none of them is constantly present and the most striking thing in the examination of such kidneys is the slight amount of disease which is often found.[1]

Casts.—Albuminous material which under various abnormal conditions has escaped from the blood-vessels in solution may solidify or coagulate, especially in the lumina of the tubules, owing to the abstraction of water and increased acidity, thus forming the more or less cylindrical or globular structures called casts. These may be homogeneous in structure —*hyaline casts;* or the albuminous material of which they are formed

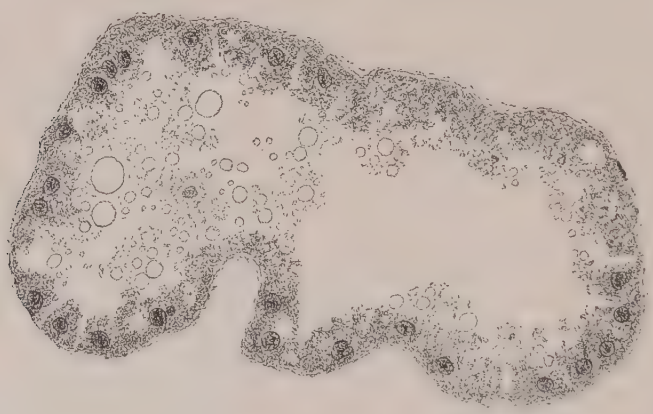


Fig. 561.—Hyaline Globules in Uriniferous Tubule.
There are also degeneration and disintegration of the epithelium.

may be mingled with the products of degeneration and disintegration of epithelial cells, either from the glomeruli or from the tubules or with red blood-cells, or leucocytes, or exfoliated epithelial cells. In this way *granular casts, epithelial casts, blood-casts,* etc., are formed. The epithelium of the tubules may peel off in masses, forming cast-like cell structures. Homogeneous globules of various sizes may be formed in the epithelium of the convoluted tubules which is yet in place, and, as the cells degenerate and disintegrate, such homogeneous globules may collect in the lumina of the tubules (Fig. 561). The exact nature of these granules is as yet a matter of discussion. They have been considered as secretory products allied to or derived from the Altmann granules, but

[1] For discussion and bibl. of the subject, see *Braasch, W. F.*, Jour. Am. Med. Assn., 1913, lxi, 936; *Spitzer, W. M.*, ibid., 1914, lxiii, 2110; and *Payne, R. L.*, Surg., Gynec., and Obst., 1916, xxiii, 76. For a discussion of these cases from a surgical standpoint, see *Payne, R. L.*, and *MacNider, W. B.*, Jour. Am. Med. Assn., 1916, lxvii, 918 (bibl.).

the weight of opinion is that they are degenerative products.[1] It is possible that they assist in the formation of hyaline casts after reaching the lumen of the tubule (Fig. 562). Homogeneous casts giving the microchemical characters of amyloid are of occasional occurrence in the tubules.

Casts and cell detritus may form both in the cortical and medullary tubules and may pass out of the organ with the urine.

NECROSIS.

Necrosis of the epithelium of the kidney of varying extent may occur in disturbances of the circulation by thrombosis, degenerations, etc., in acute infectious diseases, in various nutritional disorders, such

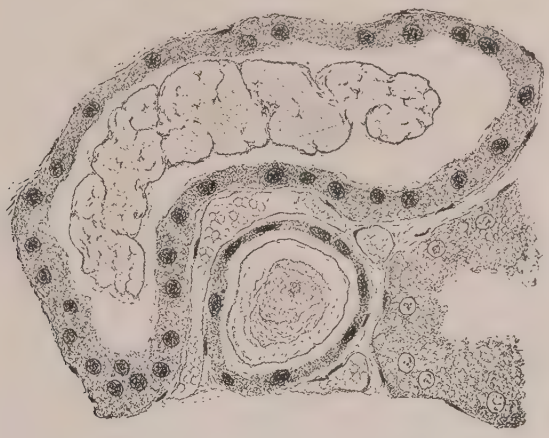


FIG. 562.—HYALINE CASTS IN URINIFEROUS TUBULE.
The epithelium is flattened in the tubules containing the casts.

as gout, diabetes, etc., or autointoxications, as well as in poisoning by various substances, cantharidin, sublimate,[2] chromates, chlorates, tartrates, salicylates,[3] uranium salts, arsenic (salvarsan), bismuth,[4] etc. In sublimate and oxalic-acid poisoning, and after prolonged roentgenization,[5] calcification (Figs. 33 and 35) may be associated with the necrotic process.

The extent of the lesion varies greatly. In some instances a large part of the epithelium of the convoluted tubules may be necrotic without marks of inflammation. In other cases the lesion involves the tubules in limited regions (Fig. 557). It is suggested that certain forms of extensive necrosis of renal epithelium are the analogues of some forms of acute yellow atrophy of the liver.[6] In fact the kidney lesion may accompany acute yellow atrophy.

[1] See, for discussion of this question, *Volhard* and *Fahr*, Die Brightsche Nierenkrankheit, Berlin, 1914.

[2] For studies on sublimate poisoning, see *Neuberger*, Zieglers Beitr., 1889, vi, 429; also *Heineke, A.*, Zieglers Beitr., 1909, xlv, 197 and *Elbe*, Virchows Arch., 1905, clxxxii, 445.

[3] *Hanzlik* and *Karsner*, Arch. Int. Med., 1917, xvi, 1016.

[4] For cases of bismuth poisoning, see *Mayer* and *Baehr*, Surg., Gynec., and Obst., 1912, xv, 309 (bibl.).

[5] *Warthin, A. S.*, Jour. Am. Med. Assn., 1907, cxxxiii, 736.

[6] For a résumé of necrosis of renal epithelium, see *Hewitt*, Bull. Johns Hopkins Hosp., 1906, xvii, 272.

DEGENERATION.

Albuminous Degeneration (Parenchymatous Degeneration—Acute Degeneration).—This form of degeneration is most common in the acute infectious diseases, such as diphtheria, scarlatina, measles, typhoid fever, yellow fever, and in many forms of septicemia, toxemia, or poisoning. It corresponds with the first stage of the simple nephroses according to Volhard and Fahr.[1] It usually accompanies similar lesions in other viscera, as in eclampsia. In moderate degrees of the lesion, the epithelium, particularly of the convoluted tubules, is swollen and more coarsely granular than normal (Fig. 563). In more pronounced lesions, in addition

Fig. 563.—Albuminous Degeneration of the Kidney (Acute Parenchymatous Degeneration). From a case of yellow fever. *a*, The swollen and granular epithelium peeling off and disintegrating; *b*, hyaline material in the lumen of the tubule.

to simple albuminous degeneration, the epithelium may become more or less filled with minute fat droplets, or the cells may disintegrate and peel off, or they may become necrotic and the nuclei fail to stain. The cell body may then undergo coagulation or disintegrate. Similar pictures are produced by post-mortem autolysis, especially after severe infections involving the peritoneal cavity, so that unless the material is obtained immediately after death, a decision as to the significance of the lesion may be difficult.

The gross appearance of the kidneys varies with the degree and extent of the degeneration. The kidney may be slightly or considerably enlarged. On section the cortex is usually thickened and pale with

[1] *Volhard* and *Fahr*, Die Brightsche Nierenkrankheit, Berlin, 1914. This valuable monograph contains a large number of observations, both clinical and pathological, on a number of nephritics studied by modern methods.

obliteration of the normal cortical markings. The capsule of the kidney is not abnormally adherent. When there are other associated or antecedent lesions in the kidney, the gross appearance of the organ varies.

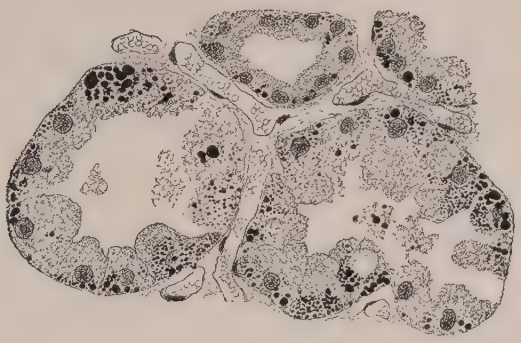


Fig. 564.—Fatty Degeneration of the Epithelium in the Convoluted Tubules of the Kidney
The fat droplets are stained black by osmic acid.

If the lesion is not too extensive, complete restitution of the kidney may take place; but if the excretion of toxic substances is long continued, vascular and interstitial changes set in which are anatomically irreparable, though the kidney may functionate normally after the lesion has subsided.

Fig. 565.—Amyloid Degeneration of Tuft Capillaries in the Kidney.
a, The tuft is completely transformed into a waxy mass; *b*, portions of tuft waxy; *c*, tuft capillaries normal; *d*, convoluted tubule with disintegrating epithelium.

Fatty Degeneration and Infiltration.—This may occur in those diseases of the blood or circulatory system in which general nutrition suffers; in infectious diseases often associated with or following albuminous degen-

eration; in various cachexiæ; in acute and chronic forms of diffuse kidney disease, and in poisoning by phosphorus, arsenic, sublimate, etc.

The degeneration may be diffuse and widespread or it may occur in patches; if it is diffuse, the cortex, in which it is most marked, is usually more or less thickened, opaque, and yellowish; if in patches there are opaque yellow streaks or spots in the cortex. But these appearances are often obscured by various other lesions. If the degeneration be moderate in degree, there are larger and smaller fat droplets, usually most abundant in the basal portion of the epithelium of the convoluted tubules (Fig. 564); but it must be remembered that a small amount of fat in the cells of Henle's loop and the distal convoluted tubules is physiological. In more marked degeneration, the cells of the convoluted tubules may be filled with fat droplets and may peel off; or they may disintegrate, setting the fat free in the lumen of the tubules. The degeneration may involve the tuft and capsule epithelium as well as that of the collecting tubes, and fat droplets may be found free or in cells in the interstitial tissue. It is not always possible in the slighter degrees of fatty change in the kidneys to distinguish between fatty degeneration and a mere fatty infiltration of the cells. It is usual to assume the latter condition unless there are other evidences of degeneration in the cells, such as alterations in the

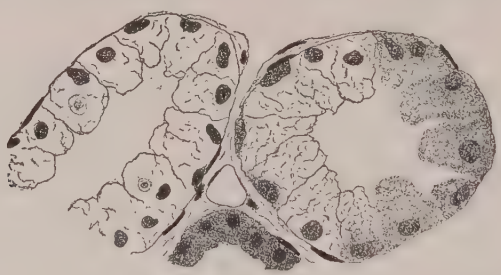


Fig. 566.—Glycogen Degeneration of the Epithelium of the Kidney in Diabetes.

nuclei, etc. The fat granules are often doubly refractile, indicating the presence of soaps or cholesterin compounds.[1]

Amyloid Degeneration.—This is usually associated with amyloid degeneration elsewhere in the body, and commonly occurs in kidneys which are already the seat of various forms of acute or chronic lesions. The capillaries of the tufts (Fig. 565) and the vasa recta are most often involved.

Glycogen Degeneration of the epithelium may take place in diabetes mellitus. It is usually most marked in the cells of the terminal portion of the convoluted tubules and the first part of Henle's loop (Fig. 566).

Calcification may occur in chronic inflammatory lesions or in old infarctions, in the papillæ, in the intertubular tissue of the medulla in the aged, and in casts in the collecting tubes, and is especially well marked in degenerated and necrotic epithelial cells in sublimate poisoning (Fig. 33 and 35).[2]

[1] *Kawamura*, Die Cholesterinesterverfettung, Jena, 1911; also *Adami*, The Myelins, etc., Harvey Lectures, 1906–07, Philadelphia, 1908, p. 117.

[2] See *Neuberger, J.*, Zieglers Beitr. 1889, vi, 429: *Heineke, A.*, ibid., 1909, xlv, 197; *Elbe*, Virchows Arch., 1905, clxxxii, 445.

The formation of bone and bone-marrow in the kidney substance may be induced experimentally by temporary ligature of the renal artery. In the human kidney, bone and marrow have been found in old infarcts and in other conditions.[1]

Pigmentation of the tubular epithelium from absorption occurs in old age, in jaundice as a deposit of bilirubin, in hemoglobinuria, and in pernicious anemia when the hemosiderin may be demonstrable only by suitable reagents. Granules of silver compounds may be found in the tube cells in argyria.

Uric Acid Deposits or, more correctly, sodium urate deposits, are found as white chalky nodules in the medullary portion of the kidney in gouty adults. An area of necrosis and inflammatory reaction surrounds the deposit and foreign-body giant cells may be found.

In infants, the so-called uric acid infarcts may be seen in the papillæ. The crystals are spherical masses of radiating structure, doubly refracting, composed of ammonium urate. Such infarcts are frequent in the newborn and have been found occasionally in the kidneys of adults suffering from leukemia and pneumonia, both diseases in which large amounts of uric acid are formed from the destruction of leucocytes. In infants at birth the blood uric acid is normal, but it increases in a few days, probably from the destruction of the nucleated red cells and leucocytes of the blood as the child adapts its circulation to postnatal conditions.[2]

DEGENERATIVE AND INFLAMMATORY DISEASES OF THE KIDNEY.

General Considerations.

In the classification which for the moment seems most practical, those lesions of the kidney in which the degenerative processes predominate are collected under the heading "Nephroses;" these may be simple or complicated with other lesions. Those lesions in which inflammatory phenomena predominate are termed "Nephritides," with the usual subdivisions of *suppurative* and *acute diffuse*. The latter may be conveniently divided into the *diffuse glomerular*, the *focal glomerular*, the *focal interstitial*, and the *focal embolic* types. All of these may pass over into *chronic* forms of nephritis as the acute inflammatory process subsides. Finally, there is a class of kidney lesions, not primarily inflammatory, which may be called *arteriosclerotic nephropathies*. The kidney alterations may be the consequence purely of arterial change—the arteriosclerotic kidney of Ziegler[3]—or the arterial degenerations may be combined with changes of an inflammatory origin producing the lesion long designated as the *true contracted kidney*. The nephritides due to tuberculosis and syphilis are, as usual, considered separately.

This classification by no means includes all types of kidney lesions which may be met with; it offers merely a series of roughly defined groups

[1] *Pearce, R. M.*, Proc. New York Path. Soc., 1908, viii, 116; *Tanaka, T.*, Zieglers Beit., 1912, liii, 338; *Pirondini*, Policlinico, 1917, xxiv, 339.

[2] See *Sedgwick* and *Kingsbury*, Am. Jour. Dis. Child., 1917, xiv, 98.

[3] *Ziegler*, Deutsch. Arch. f. klin. Med., 1879–80, xxv, 586.

in which the dominant lesions may be conveniently arranged and discussed.[1]

The processes in the kidneys which may be properly considered inflammatory are either exudative or productive, so that the apparently complex series of kidney changes which are grouped under the name nephritis or Bright's disease are really phases of *exudative* or *productive inflammation*, or of both, associated with *degenerative processes*.

Whether the kidney be large or small, white or red or mottled, smooth or rough, whether the disease be acute or chronic, it is always these comparatively simple processes, varying in extent, in duration, in intensity, and in relative predominance, which are to be taken into account in the study of inflammation of this organ.

The difficulties which are met with in the classification of renal disease are due to the fact that the various phases of inflammation and degeneration do not stand apart as independent processes or lesions, but are closely associated and often merge. It is difficult, perhaps impossible, to make a classification which shall meet the requirements of the clinic and the limitations of urinary tests, and at the same time accord with the revelations of the autopsy and the microscope.

One of the chief obstacles in the framing of a detailed classification of kidney lesions is that there are many and serious abnormalities in the function of the kidney which do not find expression in such structural changes as we can at present recognize. Our knowledge of such of the minute structural lesions in the renal epithelium as are not manifested by alterations in the size and form and organic integrity of the cell is, in fact, very meager, so that the attempt to classify inflammatory lesions of the kidney upon both clinical and morphological data often leads to conjecture or confusion, frequently to both. Neither have the hopes based upon animal experiment been fulfilled, for it has as yet proved difficult or impossible exactly to reproduce in animals some of the important renal lesions.

Considering the scope of this book, it seems wiser, therefore, to set forth as concisely as possible the essential character of the lesions in acute and in chronic phases of inflammation and degeneration in the kidney, using the morphological data as a basis, and adding only such clinical findings as may assist in the comprehension of the disease as it affects not only the kidney but the body as a whole.

The Nephroses.

Poisons or bacterial toxins present in the blood are excreted through the glomeruli, and, acting upon the renal epithelium, give rise to degenerative changes which are not strictly inflammatory in nature; hence, these lesions should not be classed as nephritis. Among the poisons which may so act are the chemical substances and bacterial products

[1] Those who are interested in the more complex phases of the question of nephritis will do well to consult *Volhard* and *Fahr*, Die Brightsche Nierenkrankheit, Berlin, 1914. For those to whom the German text is inaccessible, an excellent review and abstract with bibl., is given by *Austin, J. H.*, Progr. Med., 1915, iv, 131. See, also, *Aschoff*, Pathologische Anatomie, 1913, 3d ed., vol. ii, 429–517, for further details and good bibl.

mentioned in the previous paragraphs on necrosis and degeneration. The histological changes in the nephroses may be considered under four heads:

1. The stage of cloudy swelling;
2. The stage of extensive cellular changes;
3. The stage of reaction in the vascular connective tissue;
4. The stage of repair.

The first phase is described in the paragraph on cloudy swelling; fatty degeneration may or may not be present in the convoluted tubule. The second phase is characterized by degenerative processes in the tubular epithelium, as hyaline-drop formation, disappearance of the nucleus, and often, but not always, extensive fatty degeneration; the glomeruli are not damaged. In the third stage, the fatty degeneration of the cells of the convoluted tubules becomes more prominent. There is desquamation and, in sublimate poisoning, calcification of the cells; casts and blood are present in the tubules. Inflammation is evident in the interstitial tissue, and a few glomeruli may show a capsular hyperplasia and ultimately atrophy of the tuft. In the last stage, the active process subsides, and the formation of scar tissue begins, with the atrophy of limited areas of tubules, the glomeruli in general not being affected.

On gross examination, the kidney is seen to be congested and swollen in the first two phases; in the third it is a pale yellow with lost markings; and in the last stage it is small and mottled brown and yellow. The urine shows albumin and casts during the acute stage with retention of non-protein nitrogen. Even complete suppression is common in sublimate poisoning. In the other forms, death is due, not to the kidney lesion, but to the progression of the infection. If the patient survive the acute lesion, the late effects of the poison on the kidney may be observed in the extensive growth of connective tissue between the tubules and about some of the glomeruli. Many of the latter, however, remain intact, so the blood-pressure is not elevated and cardiac hypertrophy is missing. Very good functional repair occurs in a large majority of properly treated cases of poisoning by corrosive sublimate,[1] though even several years after restoration to apparent health traces of albumin and a few casts show that the kidney is not yet normal.[2]

The nephrosis with amyloid degeneration of the vessels is due to long-continued bacterial infections, especially chronic osteomyelitis and tuberculosis, and is, as a rule, accompanied by amyloid changes in the other organs of the body. The kidney shows the lesions just described; and, in addition, the vessels, especially the vasa recta, and tufts show extensive amyloid changes. In advanced lesions the degeneration may affect the interstitial tissue. Drop-like and fatty degenerations are often extensive. Large waxlike casts are present in the urine, but do not give the amyloid reactions (pp. 63 and 1240). The kidneys are large and pale, the cortex thick, the capsule free, and the substance firm and translucent. In the later stages there may be a diffuse growth of connective tissue with diminution in the size of the kidney.

[1] *Lambert, S. W.*, and *Patterson, H. S.*, Arch. Int. Med., 1915, xvi, 865.
[2] *Goodwin, G. M.*, Jour. Am. Med. Assn., 1918, lii, 85.

Suppurative Nephritis.

Suppurative inflammation of the kidney may follow injury with local infection. It is, however, most often due to the presence of bacteria, commonly the pyogenic cocci, which have been brought through the blood-vessels from a remote infective focus, as in ulcerative endocarditis, septic phlebitis, etc.—*embolic infection.* Or, on the other hand, the bacterial excitant may be transmitted to the kidneys through the urinary passages or their lymphatics—*ascending infection.*

Traumatic lesions of the kidney may lead to suppurative nephritis either through direct infection of the wound or by the establishment of local vulnerability to the action of bacteria which may later gain access to the injured tissue through the circulation.[1] After infected wounds or injuries of the kidney, large abscesses may develop, or nearly the whole organ may be converted into a mass of pus, blood, and disintegrated tissue.

In the *embolic type* of suppurative nephritis, small abscesses are formed most frequently in the cortex. Where bacteria lodge and grow in the tissue there is at first circumscribed hyperemia or hemorrhage and necrosis, with subsequent gathering of leucocytes and finally the disintegration of tissue and the formation of abscess. Such kidneys present to the naked eye on section small spots—or in the medulla, streaks—which are red or gray or yellow, depending upon the degree of advancement of the lesion. In such areas the bacteria may be readily demonstrated, sometimes in early stages in dense masses in the capillaries and other smaller vessels, or later scattered through the necrotic and disintegrating tissue (Fig. 127, p. 242). Embolic abscesses are commonly developed in both kidneys and by extensive coalescence may give rise to large abscesses; but in a certain number of cases the infarcts may be unilateral. This condition may be due to mere mechanical distribution of the infectious material or to a local susceptibility, the lack of ability to resist the presence of small numbers of bacteria being produced by some previous lesions, by excessive mobility, or by direct trauma. There is reason to believe that in certain forms of septicemia bacteria may secure a foothold in the tubules, not as emboli, but through excretion.[2] In such cases the suppurative foci may be at first limited to the medulla. In late phases of either type, pus may collect beneath the capsule or even break through and extend into the perirenal fat. Under certain conditions, as yet but little understood, the presence of bacteria in the glomeruli may result, not in abscess formation, but in a glomerular nephritis.[3]

Ascending Infection.—In suppurative nephritis associated with a similar process in the ureter, bladder, etc., the medullary portion of the

[1] *Cheesman, T. M.*, and *Meltzer, S. J.*, Jour. Exper. Med., 1898, iii, 533; *Brewer, G. E.*, Surg., Gynec., and Obst., 1906, ii, 485; New York Med. Jour., 1915, ci, 556.

[2] For a study of excretion of bacteria by the kidney, see *Asch*, Centralbl. f. d. Krankh. d. Harn.-u. Sex.-Org., 1902, xiii, 249, 324. See also discussion of this subject on p. 176. For a study of elimination of pigment by the kidney, see *Carter*, Jour. Am. Med. Assn., 1903, xli, 1248; *Suzuki, T.*, Zur Morphologie der Nierensekretion, Jena, 1912.

[3] *Baehr, G.*, Jour. Exper. Med., 1912, xv, 330.

kidney is usually earliest involved, and then the elongated form of the suppurative areas (Fig. 567) corresponds to the grouping of the tubules in this region.[1]

Whatever the form in which it may manifest itself, suppurative inflammation of the kidney is commonly induced by some one or combination of the pyogenic microorganisms which may lodge within it under favorable conditions. Thus Streptococcus pyogenes, Staphylococcus pyogenes, Bacillus coli communis, Bacillus pyocyaneus, Bacillus proteus, the pneumococcus, the typhoid bacillus, and others, may be found in the

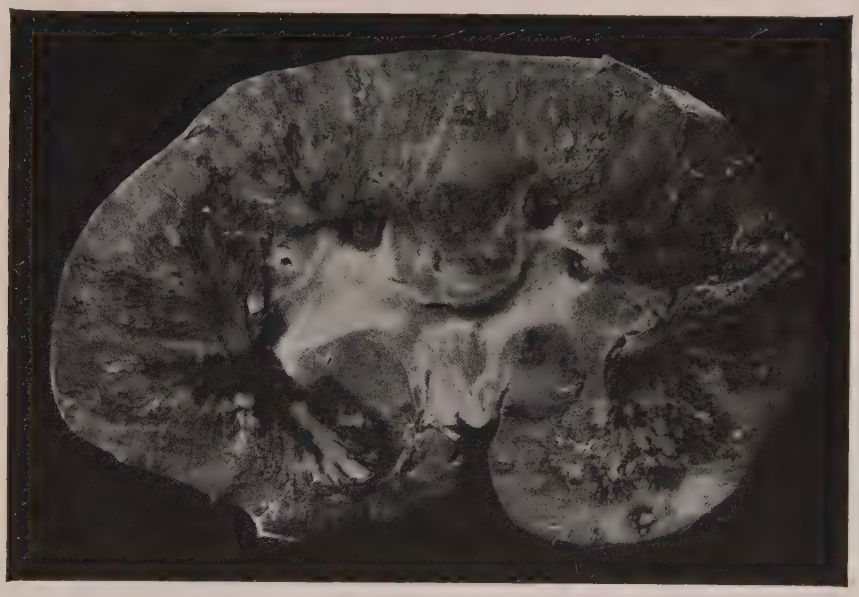


Fig. 567.—Suppurative Nephritis.
Developed from infection by way of the urinary passages (so-called "surgical kidney").

suppurative foci. Sometimes, however, especially in the more chronic processes, microorganisms are not demonstrable.

Acute Diffuse Nephritis.

This process may occur in acute infectious diseases; it is especially common in scarlatina and not infrequent in diphtheria, typhoid fever, the exanthemata, and malaria, and in septicemia due to various bacterial excitants. In a majority of instances the invasion of the infectious agent is through the tonsil.

The lesions of acute diffuse nephritis vary greatly in extent, in degree, and in the relative involvement of one or other renal structure, as well as with the duration of the process. In this, as in other forms of inflamma-

[1] For further details concerning suppurative nephritis consecutive to similar processes in adjacent organs, see p. 899.

tion of the kidney, degeneration is an important and often predominant factor in the morphology of the lesions.

We shall now consider those lesions which in varying degrees are characteristic of an early phase of acute diffuse nephritis, such as frequently occurs in the course of the acute infectious diseases. While changes in the different structural components of the kidney may occur simultaneously and are intimately related to each other, we shall study first the lesions of the *glomeruli*, second those of the *tubules*, third those of the *interstitial tissue* and its vessels.

The Glomeruli.—One of the early alterations in the tufts of the glomeruli is the swelling of the cells which cover the capillaries.[1] These cells, which in normal conditions are thin and scarcely visible, save by their nuclei, now project from the capillary loops, sometimes remaining closely apposed to the capillary walls, sometimes assuming polypoid shapes (Fig. 568), sometimes forming a continuous thick covering of cuboidal

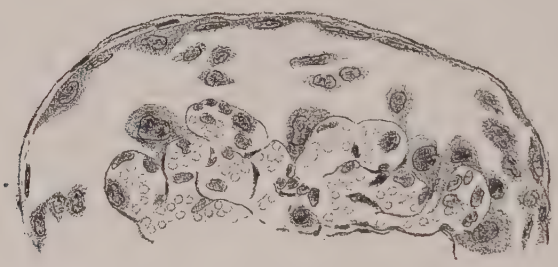


FIG. 568.—ACUTE DIFFUSE NEPHRITIS.
Showing swelling of the cells covering the capillary tufts and lining Bowman's capsule.

cells over the vessels. The nuclei are larger than normal and mitosis may be evident. Similar changes occur in the epithelium between the capillary loops. The capillaries are sometimes distended and plugged with cells; some of these are leucocytes; others are larger with large nuclei and may be swollen endothelium. Hyaline thrombi are often found in these tuft capillaries. The swollen and proliferating tuft epithelia often undergo fatty degeneration and may peel off into the glomerular space.

In some cases the proliferation and exfoliation are extensive and the cells may collect in crescentic masses within Bowman's capsule, crowding the tuft toward its hilus. The cells in these crescentic masses may be flattened from pressure and in profile appear fusiform (Fig. 569). The capsular epithelium may be swollen or remain apparently intact while there is a large cell accumulation from the tuft; or it may proliferate or become fatty or peel off. Swelling, exfoliation, and proliferation of the glomerular epithelium in some degree are of frequent occurrence in acute nephritis. They are sometimes so pronounced, especially in acute nephritis following scarlatina, either with or without extensive

[1] For a study of the development of the glomeruli and their relation to pathological changes, see *Herring, P. T.*, Jour. Path. and Bacteriol., 1900, vi, 459.

associated lesions, as to have suggested a name for one phase of the lesion —*glomerulonephritis*. There is sometimes a considerable accumulation of albuminous exudate between the tuft and capsule. Such albuminous material in specimens fixed by alcohol is in the form of fine granules and may be mingled with exfoliated and often fatty epithelium or cell detritus. If large numbers of glomeruli are involved, the blood pressure is elevated; if the number is small, as in the focal type, the pressure remains normal.

Fibrin, leucocytes, and red blood-cells may be present with other exudate within Bowman's capsule. When the fibrin and leucocytes are in excess, the lesion has been termed *fibrinopurulent glomerulonephritis;* when red cells form the predominant feature of the exudate, the term *hemorrhagic glomerulonephritis* is used.

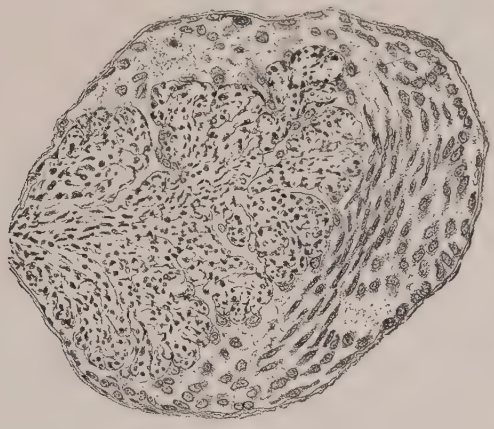


Fig. 569.—Acute Diffuse Nephritis—Following Scarlatina.

Swollen cells are seen upon the capillary tuft and lining Bowman's capsule. Polyhedral and flattened cells lie in masses between the capsule and the tuft; the latter has been pressed upon by the cells and other exudate within the capsule.

When the glomerular lesion is focal and consists in a fibrinous necrosis of the tufts apparently due to bacterial emboli, and the hemorrhagic glomeruli are sharply contrasted with the pale, edematous kidney tissue, the lesion has been called by Löhlein *hemorrhagic focal glomerulonephritis*.[1] A localized inflammatory reaction of the tubules and interstitial tissue usually occurs about the affected glomeruli. This type is seen with vegetative endocarditis due to Streptococcus viridans. When large numbers of glomeruli are involved and abscesses are formed, the lesion becomes identical with the acute suppurative nephritis type previously described.

The Tubules.—The lesions of the tubules of the kidney in the early phases of acute nephritis are largely degenerative; the epithelium, especially of the convoluted tubules, is swollen and coarsely granular (Fig. 563), or it may contain few or many fat droplets (Fig. 564)—albuminous and fatty degeneration. The epithelium may become necrotic

[1] *Löhlein*, Ergebn. d. inn. Med. u. Kinderh., 1910, v, 411; *Gaskell, J. F.*, Jour. Path. and Bacteriol., 1911–12, xvi, 287.

and may disintegrate or peel off over larger or smaller areas. Thus the lumina of the tubules may contain fragments of epithelium or detritus mingled with albuminous fluid—serum—red blood-cells and leucocytes, or hyaline or other forms of casts (Fig. 562). Red blood-cells may be extravasated in considerable numbers and collect in the tubules or pass on with the exudates. The casts and other exudates may be present in the cortex or in the collecting tubes of the kidney.

The Interstitial Tissue.—This in early phases of acute nephritis may be edematous or it may be more or less infiltrated with leucocytes or

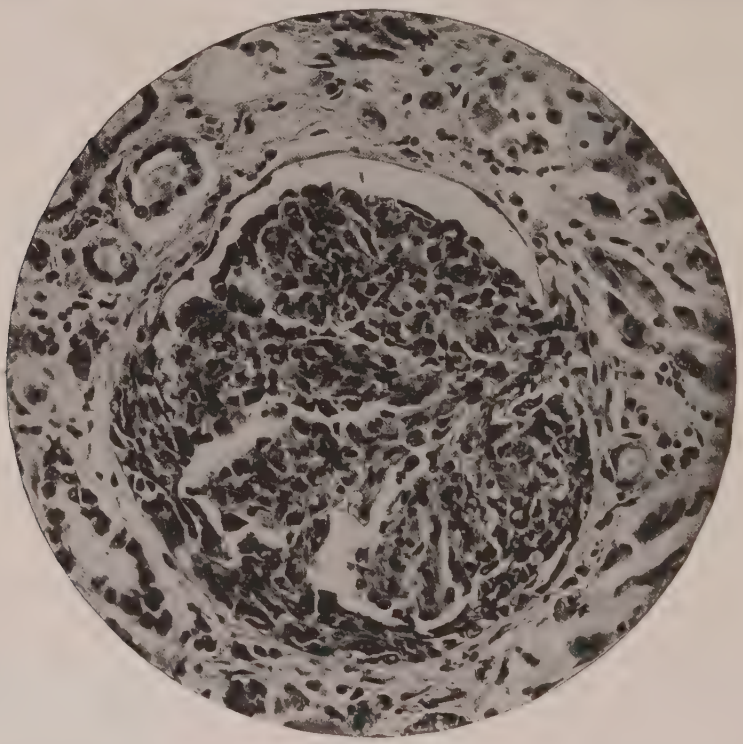


Fig. 570.—Acute Diffuse Nephritis.
Showing proliferation of cells on the tuft and lining the capsule of the glomerulus and the formation of new interstitial tissue with large polyhedral cells—glomerular and interstitial type.

fibrinous exudate. Patches of new-formed small spheroidal cells, or larger cells with conspicuous excentric nuclei may be present either in the vicinity of the glomeruli (Fig. 570) or near the interlobular veins, or a general thickening of the interstitial tissue may occur even very early in some forms of acute diffuse nephritis, particularly in those following scarlatina and diphtheria.

We have thus seen that in the early phases of an acute inflammation of the kidneys, such as may occur independently or in connection with acute infective processes elsewhere, there is an involvement of all the structural units of the organ, the glomeruli, the tubular epithelium, and

the interstitial tissue. Such a process involving the various kinds of tissue is called diffuse,[1] and the process is therefore designated *Acute Diffuse Nephritis.* This is the *acute diffuse glomerulonephritis* of Volhard and Fahr, and the *glomerulotubular* or *parenchymatous nephritis* of Aschoff.

While both kidneys are involved in acute diffuse nephritis, the lesions in each are by no means uniform either in extent or advancement and are often patchy or irregular in distribution.

Variations in Type in Acute Diffuse Nephritis.—There are many variations in the type of the lesions in acute diffuse nephritis, some of which seem to be directly dependent upon the character of the excitant, while in others the variations cannot as yet be associated with known determining conditions.

If one guard himself against the notion of distinct species in the lesions it is convenient to recognize certain structural variants or types. Thus the changes in the glomerular capillaries and epithelium may, as above indicated, be prominent—*glomerular type*—(so-called *glomerulonephritis*) (Fig. 569 and 570); the degenerative process in the tubular epithelium may be extreme—*parenchymatous* or *degenerative type;* there may with other lesions be considerable hemorrhage into the glomeruli, tubules, and interstitial tissue—*hemorrhagic type.* With or without marked structural involvement of the parenchyma and interstitial tissue there may be an exudative inflammation in which serum and leucocytes (Fig. 571) and more or less red blood-cells may gather in the glomeruli or tubules and with various forms of casts pass off in the urine. This, which is common, has been called by Delafield the *exudative type* of acute diffuse nephritis. The leucocytic exudate may collect largely about the tubules and glomeruli, giving rise to the *acute focal interstitial* type.[2] As the lymphocytic or plasma cells are not in the lumina of the tubules this type may show little or no exudate in the urine, little albumin, and no casts. Finally, with any one or more of the above types of lesion there may be early and significant involvement of the interstitial tissue of the kidney, so that new and often very cellular tissue, either in small patches or through a large portion of the organ, may lead to tubular atrophy and to serious and permanent structural alterations. This, which has been called by Delafield the *productive*

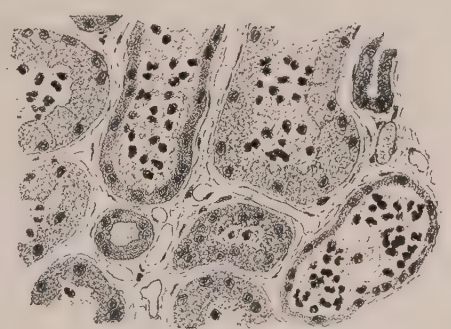


Fig. 571.—Acute Diffuse Nephritis.

Showing pus cells and granular exudate in the tubules, with flattening of the epithelium; also moderate edema of the interstitial tissue—exudative type.

[1] It should be understood that the word "diffuse" is not used in the sense of widespread or uniform, but as indicating involvement of the various structural units of the organ.

[2] See *Councilman, W. T.*, Jour. Exper. Med., 1898, iii, 393, for interesting study of "acute interstitial nephritis." Councilman regards the new cells in the interstitial tissue as largely "plasma cells" derived from lymphoid cells of the blood.

type, by others the *interstitial type*, of acute diffuse nephritis (Fig. 570), is most frequent as a complication of scarlatina; but it may follow diphtheria or puerperal infections, and may occur as an apparently independent process.

Between these types of lesion, largely based, as will be seen, upon the relative involvement of the structural units of the kidney, are many intermediate forms which the scope of this book does not permit us to consider.

Kidneys which are the seat of acute diffuse nephritis sometimes appear almost normal on gross inspection. But in more typical forms they are slightly or considerably enlarged, the capsule is free, the cortex is thickened, and either reddened or pale or mottled red and gray. When the interstitial tissue is edematous the cortex may appear translucent. The glomeruli may be red or pale and conspicuous or normal in appearance. The pyramids may seem unusually red by contrast with the thickened pale cortex. In hemorrhagic forms of acute nephritis in

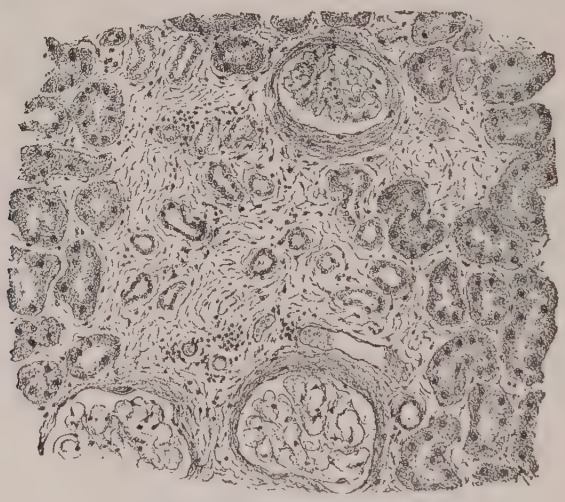


FIG. 572.—DIFFUSE NEPHRITIS.

Showing an advancing lesion following an acute type. Note the formation of a patch of dense fibrous tissue, with thickening of the walls of the glomeruli and atrophy of the tubules.

which blood may collect in the glomeruli, in the interstitial tissue, and in the tubules, the cortex may be mottled with red.

In many forms of acute diffuse nephritis, particularly if the interstitial tissue be not considerably involved, resolution may take place.

The Excitants of Acute Diffuse Nephritis.—In many cases of acute diffuse nephritis, the process seems to be due to toxic substances which are formed under the influence of microorganisms in other parts of the body and presumably excreted by the kidney with whose cells they come into intimate contact or in whose metabolism they may share. It may occur with extensive lesions of the skin and after exposure to cold. In the acute nephritis following extensive burns, exposure to cold, etc., it is

probable that the poisonous products of abnormal body-cell metabolism are the direct excitants.

Although bacteria may be eliminated from the body through the kidney sometimes without inducing lesions which are demonstrable with our present technique,[1] they usually occur only when albumin also is present in the kidney. The following bacteria have been found by numerous observers in the kidney and in the urine in acute diffuse nephritis: the typhoid bacillus, pneumococcus, streptococcus and staphylococcus, the colon bacillus, and others. The Plasmodium malariæ may be present in the kidney in large numbers.[2] To what extent the kidney lesions are due to the presence of these organisms themselves and to what extent to eliminated toxins is not yet clear.

Persistent and Advancing Lesions Following Acute Diffuse Nephritis.

If we follow the alterations which the kidney in acute diffuse nephritis may undergo if resolution do not occur but the process continue, we find that in each of the three structural units of the kidney—the glomeruli, the tubules, and the interstitial tissue, with the blood-vessels—important changes take place which often lead to slight or to marked deformities of the organ, and to such minute changes as are in fact characteristic of what we are wont to call chronic diffuse nephritis.

The capillaries of the tufts may become partly or wholly obliterated by a gradual thickening of their walls and an increase of the connective tissue between them, while at the same time Bowman's capsule is thickened and contracts upon the altered tuft (Fig. 572) with which it may unite so that the glomerulus may finally be represented by a small, dense spheroidal mass of fibrous tissue (Fig. 573).

Fig. 573.—Atrophied Glomerulus in Chronic Nephritis.
The tuft is converted into a dense mass of fibrous tissue.

The interstitial tissue of the kidney may be increased in patches, most often at first near the glomeruli or along the interlobular veins. This tissue may at first be quite cellular, resembling a collection of small spheroidal cells or larger polyhedral cells, among which new fibrillar stroma may develop; or there may be a more diffuse increase of connective-tissue cells and stroma. As this new-formed fibrous tissue grows less cellular it contracts, the tubules which it incloses are atrophied, the epithelium may undergo fatty degeneration and peel off or become flattened, casts may be present in the narrowed lumen, and the tubules may at last be represented by a small cluster of flattened cells without distinct tubular structure, or they may disappear altogether (Fig. 572). Such islets or masses of new-formed fibrous tissue inclosing variously altered and atrophied remnants of glomeruli and tubules vary greatly in size and usually merge gradually into less altered kidney tissue. When they are formed near the surface of the kidney, the shrinkage of the fibrous tissue, which is continuous with the inner layers of the capsule of the organ, may draw the surface inward, leaving between the irregular depressions the areas of less altered, or otherwise altered, kidney tissue somewhat projecting in irregular knobs or granules. Thus arise the granular surface and the adhesion of the capsule which are frequent in some forms of persistent diffuse nephritis.

[1] See *Biedl* and *Kraus*, Arch. f. exper. Path. u. Pharmakol., 1896, xxxvii, 1 (bibl.); *v. Klecki*, ibid., 1897, xxxix, 173; *Sittmann*, Deutsch. Arch. f. klin. Med., 1894, liii, 323.

[2] For a study of malarial nephritis, see *Thayer, W. S.*, Am. Jour. Med. Sc., 1898, cxvi, 560; and *Ewing, J.*, Tr. Assn. Am. Phys., 1901, xvi, 450.

In the parts of the kidney less involved, or not at all involved, in the production of new fibrous tissue, the tubules may undergo marked alterations. Thus, the epithelium may be swollen and coarsely granular or fatty; it may become necrotic so that the nucleus fails to stain; it may, when necrotic or degenerated, peel off or disintegrate so that the tubules may be extensively denuded. On the other hand, the epithelium may remain in position, but be much thinner than normal, while the lumen is largely dilated. This may take place by the blocking of the tubules below by desquamated cells or casts, or by compression of new-formed interstitial tissue. The whole tubule, not merely the lumen, may be dilated and irregular in shape, with well-preserved or fatty or otherwise altered epithelium. Casts of various forms may be present.

Chronic Nephritis.

General Considerations.—We have seen that when the inflammatory process in the kidneys, at first acute, is protracted, both the degenerative and the productive lesions may become more marked and extensive. Thus, with a preponderance now of the interstitial alterations and again of the degenerative or other changes in the parenchyma, the kidneys in a condition of chronic nephritis may present a considerable variety in gross as well as in microscopical appearance. They are sometimes larger than normal, as is often though not always the case when the parenchyma is more conspicuously involved; or smaller, as is usual when the interstitial lesions are widespread or advanced.

Although there is no sharp line of separation, either clinical or morphological, to be drawn between acute and chronic nephritis, it is convenient to group kidney lesions in this way with the understanding that many intermediate forms exist, as must be the case, since, as we have seen, acute nephritis may pass gradually into the chronic form.

While acute diffuse nephritis may be followed by the alterations which have just been summarized, and which are characteristic of certain phases of chronic nephritis, the latter process, it should be remembered, is by no means always or usually preceded by an acute form of inflammation.

Anatomically, two rough groups of chronic nephritis can be distinguished: 1, a group in which the vascular lesions predominate; and, 2, an inflammatory and degenerative group in which the tubular and interstitial lesions seem most important. These two groups can be differentiated clinically also.

1. **Vascular Type of Chronic Nephritis.**—A form of kidney lesion frequently met with is one in which the process is chronic from the onset and seems based upon primary arteriosclerotic changes in the smaller renal vessels. Cases of this type are best classified as *nephropathies of vascular origin*, and not according to current views, as of inflammatory origin. Two varieties may be distinguished: (*a*) *the arteriosclerotic contracted kidney* of the older authors; and (*b*) *the true or primary contracted kidney* or *combined type.*

(*a*) *Arteriosclerotic Contracted Kidney.*—In this type, the primary lesion is an arteriosclerotic process of the finer capillaries supplying the kidney parenchyma, which occurs late in life.[1] It results in a destruction

[1] For a discussion of the changes in the glomeruli and arteries, see *Gaskell, J. F.*, Jour. Path. and Bacteriol., 1911–12, xvi, 287.

of the glomerular tufts, which become first collapsed, and then hyaline, and, finally, lose all structure in a mass of hyaline connective tissue with occasional scattered nuclei. The tubules derived from such glomeruli atrophy and are replaced by connective tissue. Casts may be present in the tubules so long as their lumina are patent. The kidney tissue independent of the thickened vessels remains healthy. In this early state there is no contraction of the kidney, the markings of the cortex are preserved, and the capsule strips with ease, leaving a fairly smooth surface, the only gross lesion being a lobulation of the surface. The consistence of the organ is firm, the color a dark red. Later, when the changes are more extensive, the kidney contracts; the capsule is adherent; the surface is granular, because of the shrinking of the connective tissue from the still functionating tubules; the cortex is narrow (3 to 4 mm.); and the thickened vessel walls protrude from the cut section as empty rigid tubes. The markings of the cortex still remain fairly clear. The renal lesion is usually accompanied by extensive vascular sclerosis elsewhere. The blood pressure is regularly high; the heart is hypertrophied; and a moderate amount of polycythemia is not infrequent. The urine is normal, except occasionally, when a little albumin and a few hyaline casts may be present. Large quantities of albumin and edema point either to cardiac failure or to the onset of inflammatory changes in the kidney. The permeability of the kidney for chlorides, urea, and dyes is diminished only in the later stages, but not so markedly as in the next form described, for a certain number of kidneys of this type may give so few symptoms that the existence of the lesion can not be demonstrated except at autopsy. A terminal uremia is rare; death is usually due to cardiac decompensation, pneumonia, or apoplexy.

Nevertheless while, as has been said, many persons with arteriosclerotic kidneys may show no symptoms of the lesion, and, in fact, be capable of heavy manual labor, careful functional tests will usually reveal some alterations in the capacity of the organ. About one-half of the cases will from time to time show a slight retention of urea and have a systolic pressure over 160; at least a quarter of the cases have traces of albumin in the urine; and practically all show occasional hyaline casts. The phenolsulphonephthalein excretion also is slow. Persons with these lesions may remain in health for a long time, unless subject to an acute infection, in which case the symptoms are often almost entirely those of renal insufficiency with large amounts of albumin, casts, and edema.[1]

(*b*) *Combined Type or True Contracted Kidney.*—In this form vascular changes are combined with inflammatory lesions of the glomeruli and tubules, and the disease is seen in younger people. As a result of the inflammatory changes, the markings of the cortex are lost, in contrast to the previous type; and the color of the cut surface is reddish with numerous yellowish stripes or spots. Cysts may be present on the surface. The capsule is moderately adherent, the surface finely granular, the granules being due in part to the projections of areas of regeneration of the surface tubules. The glomeruli are in part atrophied, as in the

[1] *Rappleye, W. C.*, Boston Med. and Surg. Jour., 1918, clxxviii, 191; 1918, clxxix, 441.

pure vascular type; but, in addition, they may show inflammatory and degenerative lesions. Fatty degeneration of the tuft epithelium is frequent. Leucocytes, as well as red blood-cells, may be present in the capsular space. Crescentic capsular cell masses may be found as in acute glomerular nephritis. The cells of the convoluted tubules are often fatty and may show drop-like degeneration. The inflammatory process may also extend to the interstitial tissue. But all these acute or subacute lesions may, in some instances, be quite focal. Clinically, the disease runs a much more active course than the arteriosclerotic form. Very high blood pressure[1] and cardiac hypertrophy are constant; anemia is the rule; and terminal uremia is frequent. Neuroretinitis albuminurica is very often observed. In the early stages, albumin and casts may be small in amount, later they are regularly present in abundance. Epithelial casts and fatty tubular epithelium are occasionally seen. Nycturia and polyuria are the rule. As the chlorides are retained, edema is frequent. Creatinin, urea, and non-protein nitrogen are found in increased quantities in the blood after the disease becomes active. The permeability for dyes is much diminished. Death is due to cardiac decompensation or uremia. This is the form of kidney lesion which in its terminal stages is often clinically called an acute nephritis.

2. Inflammatory and Degenerative Type of Chronic Nephritis.—In addition to the forms of nephritis just described, in which the vascular lesions dominate the clinical picture and morphological findings, it is convenient to place in one group those kidneys in which, although there may be important changes in the glomeruli and the interstitial tissue, the most marked lesions are in the tubular epithelium. This may be conveniently called the *parenchymatous* or *degenerative* type of chronic diffuse nephritis.

On the other hand, there is another large and important class of kidneys which are characterized morphologically by a relatively prominent increase in the amount of *interstitial fibrous tissue* with associated destruction by atrophy or otherwise of the tubular structures. This may be called the *interstitial type of chronic diffuse nephritis.*

In considering this, in many respects artificial, grouping of persistent inflammatory kidney lesions, it should be remembered that while the parenchymatous and the interstitial types of lesion may originate as such and so persist, the lesion of the parenchymatous type may, as the disease progresses, assume the characters of the interstitial form.[2]

(*a*) *Parenchymatous Type of Chronic Nephritis.*—This may originate in an acute diffuse nephritis, but more frequently develops independently of this or, at least, without any clinical history of previous renal disease. As in other forms of diffuse nephritis, the tubules, the glomeruli, and the interstitial tissue are more or less involved. The lesions are most marked in the cortex (Fig. 574), and here the epithelium may be swollen and

[1] For a study of nephritic hypertension, see *Janeway, T. C.*, Am. Jour. Med. Sc., 1913, cxliv, 625. For experimental studies on the relationship between destruction of renal parenchyma and cardiac hypertrophy, see *Pässler* and *Heineke*, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 99.

For a study of subacute and chronic nephritis, see *Ophüls, W.*, Arch. Int. Med., 1912, ix, 156; for a study of classification, see *Oertel, H.*, ibid, 1913, xi, 653.

coarsely granular or often fatty. Droplets of clear fluid may form within the epithelium—so-called drop-like degeneration. The epithelium may be flattened or it may peel off or disintegrate, and the cells and cell detritus together with leucocytes, red blood-cells, and casts may collect in the irregular and often widened lumina. The casts may be hyaline or granular or epithelial, or they may be covered with leucocytes or red blood-cells. In the glomeruli, the tuft and capsule cells may swell and proliferate and peel off (Fig. 575); albuminous fluid, which in specimens hardened in alcohol is represented by a granular precipitate, may be present in the intracapsular space and in the tubules. The interstitial tissue may be increased in amount, usually in circumscribed regions, and

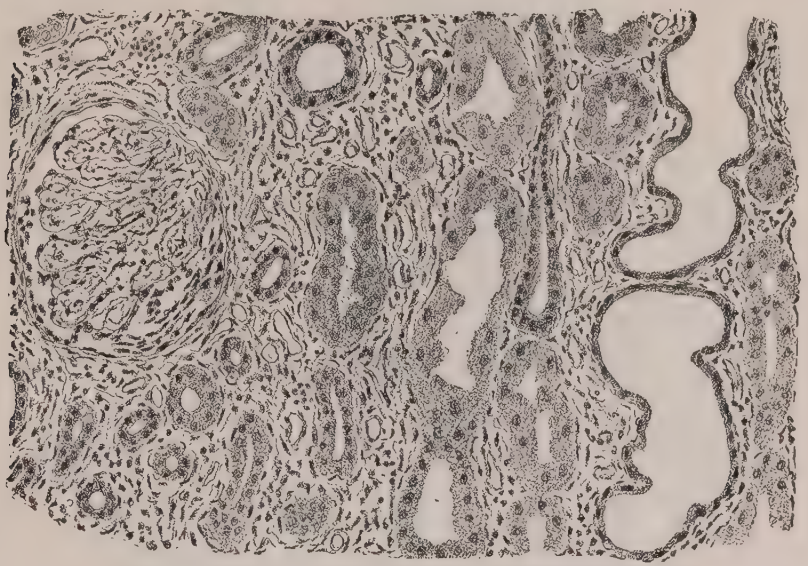


Fig. 574.—Chronic Diffuse Nephritis—Parenchymatous Type.

At the left is a band of new-formed fibrous tissue with atrophy of tubules and swelling and proliferation of the capsule cells; in the central portions the tubular epithelium is disintegrating at the edges, while at the right the lumina of the tubules are dilated, with flattening of the epithelium.

here the inclosed tubules are atrophied. Not infrequently more or less extensive hemorrhages occur.

If the disease have been of long standing the new-formed interstitial tissue may be present in considerable amount with much destruction of the tubules. The glomeruli may be compromised by the thickening of Bowman's capsule and the obliteration of the capillaries, so that at length the tuft and capsule may fuse and the glomeruli may be represented by dense fibrous nodules (Fig. 573). The growth of interstitial tissue in patches may, when near the surface of the organ, bind the capsule to the kidney so that in its removal small masses of the parenchyma may be stripped off, leaving a rough surface on which grayish depressed areas, corresponding to the interstitial growth, are intermingled with more projecting light or yellowish portions, in which albuminous or fatty degen-

eration of the tubular epithelium may be marked and extensive. Very often the new fibrous tissue develops along the course of the interlobular vessels so that cylindrical or narrow wedge-shaped areas are affected, extending inward from the capsule (Fig. 576). Amyloid degeneration involving the capillary tufts, the vasa recta, and the larger arterial trunks is common.

Such kidneys as have just been described present varying gross appearances which are dependent upon the character, extent, and distribution of the lesions. In general, they are firm, and the capsule is smooth and lightly but widely adherent. The surface may be smooth or finely granular. Some are larger than normal with a thickened

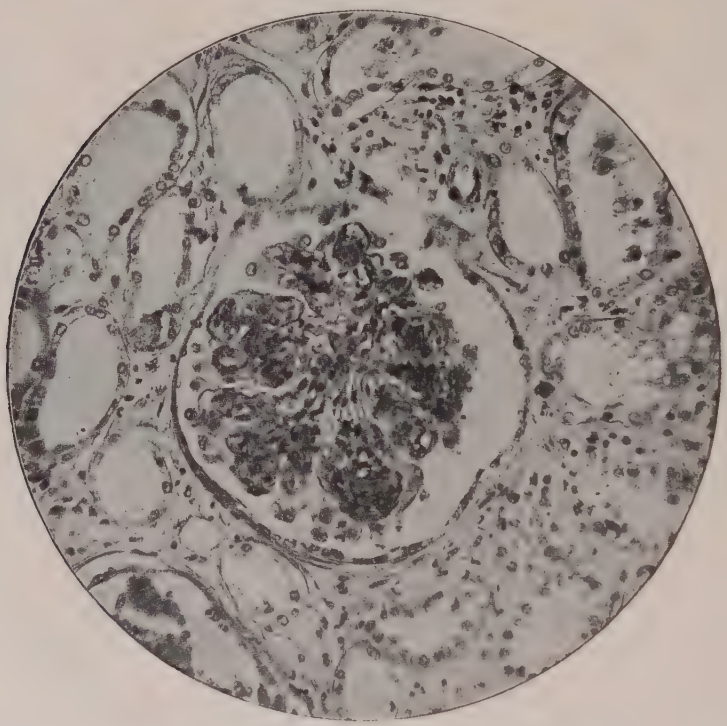


Fig. 575.—Chronic Diffuse Nephritis.
Showing swelling of tuft and capsule epithelium; flattening of the tubular epithelium and slight increase in the interstitial tissue.

whitish or yellowish cortex. These are often called *large white kidneys.* But kidneys with essentially similar lesions are not always large, and are often nearly normal in appearance; or they may be smaller and have a cortex thinner than normal. These include the *chronic parenchymatous* or *secondary contracted kidneys* of the older authors, or *nephrocirrhosis glomerularis* of Aschoff, which in their more advanced stages with extensive vascular changes can not be distinguished from the *true contracted kidney,* the lesions of which are primarily arterial and not inflammatory in character. If hemorrhage into the tubules or interstitial tissue be a

marked feature of the lesion, the cortex may be reddish or mottled red and yellow. Such are the so-called *large red kidneys.*

Arteriosclerosis and cardiac hypertrophy may accompany this type of kidney lesion, especially in the later stages. With these changes the urine, which in the earlier phases is concentrated, highly albuminous, and full of casts, becomes more abundant and of low specific gravity, and contains but traces of albumin and only few casts. Edema, with salt, creatinin, urea, and non-protein nitrogen retentions, may appear in either phase, but is extensive only in the late stages when serious failure of the heart is added to the nephritic insufficiency.

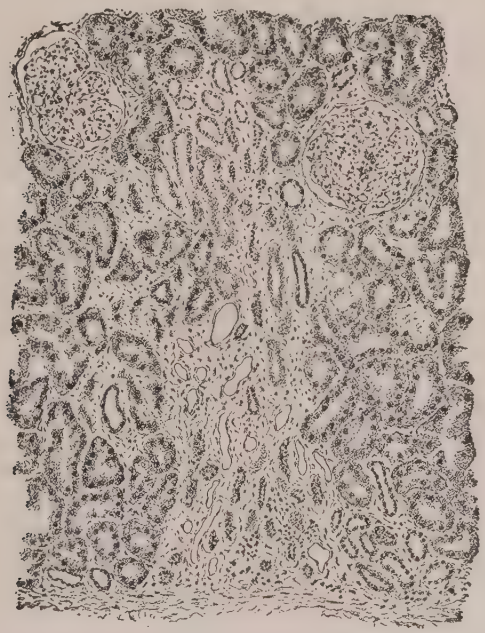


FIG. 576.—CHRONIC DIFFUSE NEPHRITIS—PARENCHYMATOUS TYPE.

Showing a wedge-shaped mass of new-formed tissue extending inward from the capsule of the kidney, to which it is firmly attached. The tubules within the fibrous area are atrophied, while the tubules elsewhere show various degenerative epithelial changes.

(*b*) *Interstitial Type of Chronic Nephritis.*—The type of chronic nephritis in which the growth of interstitial tissue is conspicuous, the *interstitial* or *indurative* type, apparently sometimes represents a later phase of the parenchymatous type, but appears to be more frequently an independent process. As the new interstitial tissue which is formed in patches or streaks or large masses gradually becomes less cellular and more dense, and shrinks, the kidneys are usually smaller than normal and, owing to the uneven distribution of the lesion, are rough upon the surface when the thickened and adherent capsule is stripped off. The areas of the cortex in which the fibrous tissue is most abundant (Fig. 577) are grayish or translucent and depressed, while the parenchyma between,

often fatty, projects as yellowish rounded knobs or granules. This condition is therefore sometimes spoken of as "granular atrophy," and such kidneys are often called "granular kidneys" or "atrophied kidneys." The tissue is firm and resistant to the knife; and on section the cortex is seen to be in general thinned, often extremely so, some portions being much more atrophied than others. Small cysts of various sizes may be formed from dilatation and coalescence of tubules. The cortex is usually more involved than the medulla. The fat with which the kidney is surrounded is often largely increased.

On microscopical examination new-formed interstitial tissue is found sometimes in patches (Fig. 577) or streaks along the course of the interlobular vessels, with less affected regions between them. In these

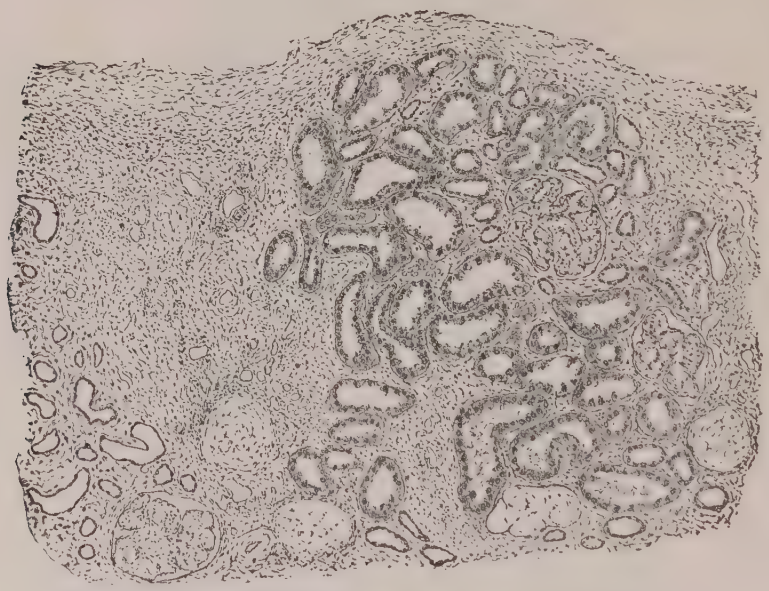


Fig. 577.—Chronic Nephritis—Atrophied Kidney—Vascular Type.

The capsule is thickened and adherent, especially to the dense mass of fibrous tissue at the left of the section, in which the tubules are greatly atrophied. At the right the parenchyma is less atrophied, but here the lumina of the tubules are dilated, the epithelium is degenerating and flattened.

fibrous portions there may be flattening of the epithelium and various degrees of atrophy or complete destruction of the epithelium and the tubules. Between these fibrous regions, slightly altered tubules may be present, or others with granular and fatty degeneration, exfoliation, and disintegration of the epithelium. Various forms of casts may be present in the tubules; the epithelium may be flattened, with enlargement of the lumen. The glomeruli are variously altered; thus there may be thickening of the capillary walls and of Bowman's capsule (Fig. 577), increase and exfoliation of the tuft and capsular epithelium, or a more or less complete conversion of the glomerulus into a knob of dense fibrous tissue. Occasionally there is partial or complete atrophy of the tuft with more

or less dilatation of the capsule. Thus small cysts are formed lined with flat cells and containing a homogeneous or granular fluid and sometimes small masses of calcium salts.[1]

In advanced phases of the lesion the kidney may be very small; then a large part of the tissue is involved; and while the atrophy is always more marked in some places than in others, it is often difficult to find any normal structural elements.[2]

Fibrous thickening of the walls of the arteries and veins of the kidneys is usual in this type of chronic diffuse nephritis. Amyloid degeneration of the vessels is not infrequent. The heart is often greatly hypertrophied, and general arteriosclerosis is common.

The Excitants of Chronic Nephritis.—The conditions under which chronic nephritis occurs are most diverse. Thus, judging from the clinical history, it may be a primary process; it may follow infectious diseases either with or without a previous acute nephritis; it is not infre-

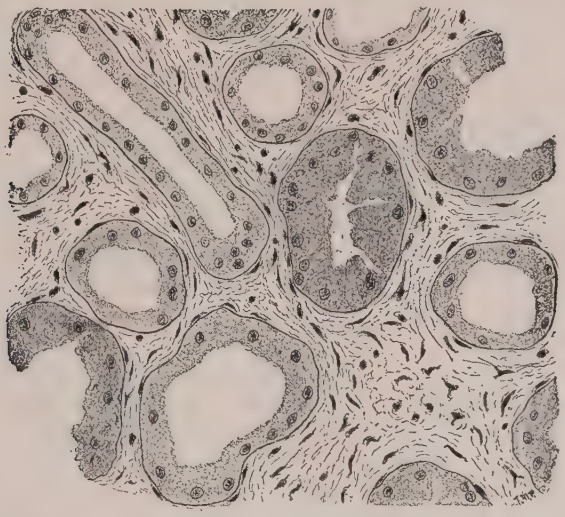


Fig. 578.—Chronic Nephritis.
Showing interstitial tissue, dense and fibrous in type, between the tubules. The epithelium is in part flattened; in places shows albuminous degeneration.

quently associated with gout and syphilis, with lead poisoning, with excessive use of alcohol, with general arteriosclerosis, with general chronic congestion of the viscera and with chronic suppurative and tuberculous processes, and appears in many cases to develop under the influence of dietetic excesses and protracted gastrointestinal disorders. The nature of the excitants under these various conditions is most obscure. Although in gout, lead poisoning, alcoholism, etc., a fairly definite inciting toxic agency may be assumed, the exact mode of action of such extrinsic or intrinsic poisons is almost wholly unknown. In regard to other exci-

[1] For a study of atrophic glomerular cysts, see *Beer, E.*, Am. Jour. Med. Sc., 1904, cxxvii, 611.

[2] For a résumé of views on the nature and origin of the contracted kidney, see *Aschoff, L.*, Cartwright Lectures, Arch. Int. Med., 1913, xii, 723.

tants of chronic diffuse nephritis, the prevalent views as to the importance of disturbed metabolism in the body which may lead to the excretion of abnormal harmful products favor the conjecture that in many cases at least both the degenerative and the productive processes may be the marks of a persistent autointoxication.

The reason for our lack of definite information as to the agents causing chronic nephritis is that the experimental production in animals of nephritis of the type which occurs in human beings, though long attempted, has hitherto had no great success. The lesions produced, while distinctly nephritic, vary considerably from those seen in man.[1]

It must be remembered also that the renal lesion in chronic nephritis is only a part of the picture. The vascular changes are possibly the precursors of the renal and as our knowledge of the underlying causation of arteriosclerosis is limited, this ignorance involves the kidney lesion also. Hypertension is believed to be a cause of arterial lesions, but we as yet know little concerning the agencies inciting hypertension.

It has recently been shown however that by exposing the kidneys of dogs to large quantities of X-rays a variety of lesions can be produced. In four or five days after irradiation the kidney is swollen and congested; the blood-vessels are dilated and engorged and intertubular hemorrhages are numerous. The lining epithelium is swollen, granular and poorly staining. It may separate entirely from the basement membrane. The glomeruli are engorged and fill the capsule. In many of them there is extravasation of the blood from infiltration by small cells. In four to eight weeks after the exposure to X-ray, lesions of a subacute variety can be made out. The tubules are distended and widely dilated with flattened atrophic epithelium. The lumen may contain homogeneous pink-staining material. The glomerular tufts show hyaline changes. After three months lesions of a chronic type appear, in which, while the glomeruli are relatively well preserved the blood-vessels show marked changes, the epithelium of the tubules extensive degenerative changes, and there is as a terminal process an increase in interstitial connective tissue with sclerosis. Morphologically these kidneys resemble human chronic nephritis. Functional studies show a diminished dye excretion, with albumen and casts, and a marked polyuria with low specific gravity. The blood-pressure is raised and there are flame-shaped hemorrhages in the retina. The terminal stages of the disease are characterized by ascites, convulsions and other clinical symptoms of complete renal incompetence.[2]

FUNCTIONAL PATHOLOGY OF NEPHRITIS.

During the last twenty years the study of the function of the kidney has led to the accumulation of much information of value in the prognosis and treatment of kidney lesions, but the results so obtained do not as yet permit of an accurate correlation between the existing anatomical lesion and the clinical symptoms. Certain symptoms, such as edema, high

[1] *MacNider*, Experimental Nephritis, Physiol. Reviews, 1924, iv, 595.
[2] *Hartman*, *Bolliger* and *Daub*, Am. Jour. Med. Sci., 1926, clxxii, 487.

blood-pressure, etc., have been mentioned during the discussion of the lesions; but a short résumé of some of the results of chemical and functional tests may be of interest here.

The presence of albumin, casts, and blood-cells in the urine is still the most delicate indicator we have of a renal lesion, but offers little information as to the extent and nature of the changes in the kidneys. In general it may be said that the severe nephroses show large quantities of albumin and numerous casts, with a reduction in the quantity of urine, even to complete suppression, and the accumulation in the blood of large amounts of solid matter, especially urea and sodium chloride. The same is true of the acute nephritides. Edema is not infrequent in the nephroses, common in the nephritides.

The history of poisoning or the demonstration of an existing or recent infection are important points in determining the nature of the lesion. For example, the appearance of the kidney in a case of poisoning by corrosive sublimate is quite as characteristic as the glomerular nephritides of scarlatina or bacterial endocarditis.

The chronic forms of nephritis offer the greatest difficulties in interpretation. The purely arteriosclerotic kidney with the concomitant high blood-pressure and scanty albumin and casts, the excretory power being otherwise fairly good, can be recognized in many instances. The anatomical changes underlying the chronic secondary types and the combined arteriosclerotic-nephritic forms can not at present be determined with any accuracy. The tendency is, for clinical purposes, to separate chronic nephritis into three rough groups: (1) Cases with salt retention, usually accompanied by edema. (2) Cases with nitrogen retention, which are less apt to show edema if the cardiac function is good; and, (3) the combined forms.[1]

These groups do not necessarily correspond to the anatomical forms of nephritis which have just been described. The complexity of the lesions and our lack of methods for testing the functional deficiencies of the various portions of the glomerulus and renal tubule as yet prevent such correlation.

The methods for making the functional tests and the interpretation of the results can be referred to here only in brief. They include the determination by chemical means of the amount of urea, sodium chloride, and creatinin present in the blood, these substances, if present in excess, representing the summation of the kidney deficiencies on a normal diet. The momentary deficiency in excretory power is best estimated by the phenolsulphonephthalein test.[2] The excretion of this substance may be normal when other substances are retained, showing an as yet unknown difference in the selective excretion of the kidney. Also, the urea, for example, may not be retained in excess and yet a slowing of its output may exist as shown by a comparison between the amount in the blood and the amount excreted in the urine. This ratio expressed numerically

[1] For a discussion of this classification, due largely to the French school, see *Ambard*, Phys. Normal et Pathologique des Reins, Paris, 1914.

[2] *Rowntree* and *Geraghty*, Jour. Pharmacol. and Exper. Therap., 1910, i, 579.

and taking into account the patient's weight, is the *Ambard coefficient.*[1] Finally, the urinary constants are determined with the patient on a standard diet[2] with or without the addition of known amounts of urea or sodium chloride. Useful results may occasionally be obtained by the use of a diuretic. With the help of these methods, the existence of a mild functional disturbance of renal excretion can be detected as exemplified in a preceding paragraph on arteriosclerotic kidneys.

A separation can often be made between cardiovascular disease in which the chronic congestion of the kidney incites the passage of traces of albumin and a few casts and thus simulates nephritis, and true renal disease with secondary cardiac failure. In the former, the kidney still performs its excretory functions well; in the latter, some one of the tests mentioned will usually reveal a renal insufficiency.

These tests also permit of the demonstration, otherwise impossible, of an insidious progress of the kidney lesion to the final stage of utter refusal to excrete the toxic end results of protein decomposition, with the ultimate appearance of acidosis[3] and a terminal uremia.[4]

Tuberculous Nephritis.

Miliary tubercles may be present in the kidney in general acute miliary tuberculosis or in a localized tuberculous inflammation which is most marked elsewhere. Renal tuberculosis is, however, most often associated with tuberculous processes in other parts of the genitourinary tract. It is not infrequently primary in the kidney and is then often unilateral. If only one kidney be involved the other may become the seat of chronic diffuse nephritis with waxy degeneration of the walls of the arteries. Tuberculous inflammation may occur in a kidney already the seat of chronic inflammatory changes.

The process is apt to begin in the mucous membrane of the pelvis and calyces, and extend from thence first to the pyramidal and afterward to the cortical portion of the kidney.[5] In the mucous membrane of the pelvis and calyces there is a growth of new cellular tissue studded with tubercle granula, while the epithelial cells proliferate, become deformed, and desquamate. This process is often soon followed by cheesy degeneration of the inflammatory products. Similar changes occur in the kidney which may become extensively involved and largely destroyed. The portions of the organ which do not share directly in the tuberculous

[1] See *Ambard*, Phys. Normal et Pathologique des Reins, Paris, 1914; *McLean, F. C.*, Jour. Am. Med. Assn., 1916, lxvi, 415; Jour. Exper. Med., 1915, xxii, 212.

[2] For dietary methods, see *Schlayer* and *Hedinger*, Deutsch. Arch. f. klin. Med., 1914, cxiv, 120; *Mosenthal, H. O.*, Arch. Int. Med., 1915, xvi, 733; and *Christian, H. A.*, Jour. Urol., 1917, i, 319.

[3] *Peabody, F. W.*, Arch. Int. Med., 1914, xiv, 236; ibid., 1915, xvi, 955.

[4] For further information on this subject, see *Hinman, F.*, Internat. Abstracts Surg., 1914, xix, 465 (bibl.); *Kahn, M.*, ibid., 1917, xxiv, 449 (bibl.); *Christian, Frothingham, O'Hare,* and *Woods*, Am. Jour. Med. Sc., 1915, cl, 657 (bibl.); *Janeway, T. C.*, ibid., 1916, cli, 157; *Christian, H. A.*, ibid., 1916, cli, 625 (bibl.). For the surgical aspects of these tests, see *Braasch, N. F.*, and *Thomas, G. J.*, Jour. Am. Med. Assn., 1915, lxiv, 104; *Rowntree, L. G.*, Am. Jour. Med. Sc., 1914, cxlvii, 352.

For a general review, with bibl., see *Karsner, H. T.*, Jour. Lab. and Clin. Med., 1916, i, 910; and *Thomas, B. A.*, and *Birdsall, J. C.*, Jour. Am. Med. Assn., 1917, lxix, 1747. For a study of prognostic relations of blood constituents to renal disease and surgery, see *Squier, J. B.*, and *Myers, V. C.*, Jour. Urol., 1918, ii, 1.

[5] For a study of ascending urogenital tuberculosis, see *Baumgarten*, Arb. Path. Anat. Inst. Tübingen, 1906, v, 372; also *Kappis*, ibid., p. 379.

process often develop lesions of the interstitial type of chronic diffuse nephritis or of suppuration. Thus the kidney may become hollowed out into a series of ragged cavities with caseous and disintegrating walls (Fig. 579). Sometimes the process comes to a standstill, and then the caseous portions may be infiltrated with salts of lime.[1] The ureters and bladder are frequently involved in the later stages of the disease.

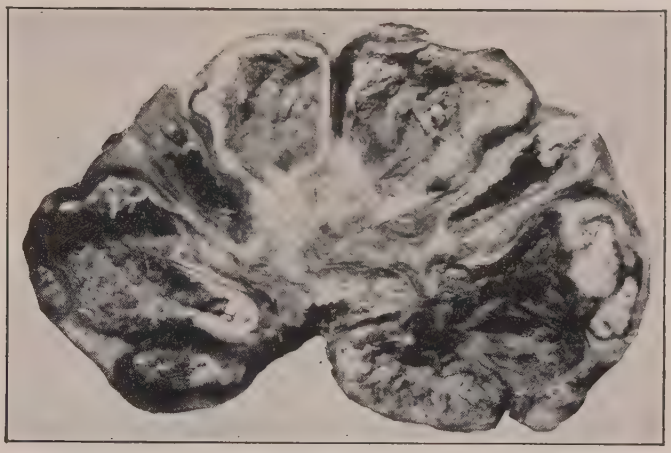


Fig. 579.—Tuberculous Nephritis.

Syphilitic Inflammation.

An acute nephritis may arise in the course of an active syphilitic infection.[2] Gummata of the kidney are of occasional occurrence. A close relationship between syphilitic arteritis and atrophied forms of chronic diffuse nephritis seems probable.[3]

SUPPURATIVE PYELITIS AND PYELONEPHRITIS.

Suppurative pyelitis is often associated with suppuration of the kidney substance, more frequently with a similar process in the bladder or ureters. But it may occur by itself without bladder or ureteral involvement, especially in female infants or young children.[4] Cystitis is a usual complication in the male. The lesion is frequently bilateral. It is incited by the same microorganisms as are concerned in the induction of the associated lesions in the kidney and bladder, in the latter case most often the Bacillus coli communis, the Streptococcus pyogenes, and the Staphylococcus pyogenes. The first mentioned organism is most frequent in the pyelitis of children and is probably introduced from the bowel through the blood or the lymph-channels, though the greater frequency of the disease in females suggests that the portal of entry is the urethra.

The mucous membrane of the pelvis may be congested or hemorrhagic,

[1] For a study of renal tuberculosis, see *Walker*, Johns Hopkins Hosp. Rep., 1904, xii, 455.
[2] *Munk, F.*, Berl. klin. Wchnschr., 1913, l, 1416.
[3] For bibliography, see *Delamare*, Gaz. d. Hôp., 1900, lxxiii, 425.
[4] *Smith, R. M.*, Amer. Jour. Dis. Child., 1916, xii, 235; *Quinby, W. C.*, Jour. Am. Med. Assn., 1917, xviii, 591.

thicker and more opaque than normal, and coated with pus or with patches of fibrin. The presence of pelvic calculi is to be regarded as a predisposing rather than as a direct inciting agent in suppurative pyelitis.

The path of invasion of the kidney substance from the pelvis is through the interstitial tissue of the pyramids. The bacteria then invade the veins or in the upper portion of the medulla pass from the invaded vessels to the Henle's loops.[1]

Suppurative Ureteritis.—The conditions under which suppurative inflammation of the ureter occurs are similar, as is the general appearance of its mucous membrane, to those just indicated in the pelvis.

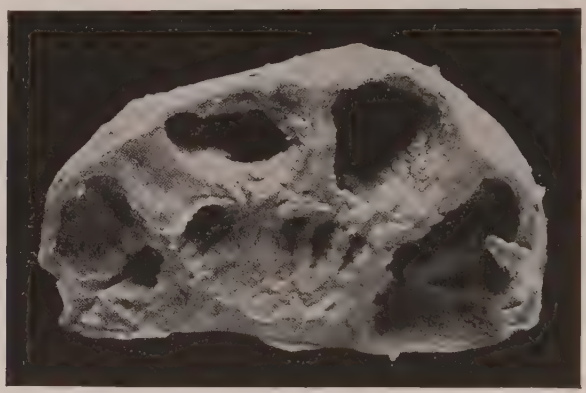


FIG. 580.—CHRONIC PYELONEPHRITIS.
Showing dilatation of the pelvis and calyces.

Suppurative Pyelonephritis with Cystitis.—In this association of lesions of the bladder and kidneys, which is usually initiated by the inflammation of the bladder, the affection of the kidneys is commonly bilateral. The suppurative areas in the kidney may be in the form of small abscesses scattered through the kidneys, or in the form of elongated whitish streaks or wedges between the tubules (see Fig. 567). The purulent foci are often surrounded by a red zone of congestion.

The kidney tissue in the vicinity of the abscesses may be necrotic, the outlines of the cells being preserved but their nuclei absent or not revealed by the usual staining agents.

The infective agent often traverses the ureters in passing from the inflamed bladder to the kidneys, leaving the mucous membrane of the ureter intact. The path followed in such ascending infections seems to be most often lymphatic, an extensive network of lymphatic vessels existing in the walls of the bladder, the ureter, and the substance of the kidney.[2] If bacteria are introduced into the bladder, they may pass up the ureter and involve the pelvis, giving rise to an acute lesion; or they may enter the kidney and either involve that organ or pass to the perirenal fat.[3]

[1] *Ribbert, H.*, Virchows Arch., 1916, ccxx, 294.
[2] *Kumita*, Arch. f. Anat., 1909, Suppl.; *Bauereisen*, Ztschr. f. gynäk. Urol., 1911, ii, 235.
[3] *Sweet* and *Stewart*, Surg., Gynec., and Obst., 1914, xviii, 460; *Eisendrath* and *Schultz*, Jour. Med. Research, 1917, N. S. xxx, 295; Jour. Am. Med. Assn., 1917, lxviii, 540.

Chronic Pyelonephritis.—Chronic cystitis or calculi in the pelvis of the kidneys may set up a chronic inflammation which involves both the pelvis and calyces and the kidney tissue. The mucous membrane of the pelvis and calyces is thickened, the epithelial layer is changed in morphology by the inflammation, or may partially desquamate. There is a growth of granulation tissue beneath the epithelium, and there may be little polypoid outgrowths. Usually collections of lymphocytes are found in the mucous membrane and the papillæ, and a general infiltration with these cells and pus cells may be noted. The surface of the mucous membrane is coated with pus or fibrin, or the cavity of the pelvis and calyces is dilated and distended with purulent serum (Fig. 580).

The kidney itself is the seat of a chronic interstitial inflammation with the production of new connective tissue, and sometimes of pus, with obliteration of the renal tubules.

HYDRONEPHROSIS.

Hydronephrosis may occur congenitally in consequence either of absence of the ureters or of obstruction of any portion of the genitourinary tract. When bilateral, it is, of course, incompatible with life. Acquired hydronephrosis may be due to a variety of causes which induce reverse hydrostatic pressure on the kidney. Among these causes may be mentioned malformations, such as horseshoe kidney,[1] spurs or valves in the pelvis of the kidney, kinking of the ureter from movable kidney, inflammatory lesions of the mucous membrane of the pelvis, ureter, or urethra, compression of the ureters or pelvis by tumors in these organs or by tumors of other organs, such as the rectum, bladder, prostate, or uterus; even by enlargement of the pregnant uterus. Narrowings or strictures of the ureter or urethra, prostatic hypertrophy, phimosis, inflammatory lesions of the bladder, ureter, or urethra, or calculi may also act as causative agents. Finally, hydronephrosis may be induced by accidental ligature of the ureter in the course of a surgical operation.[2] The amount of hydronephrosis and the ultimate change in the kidney vary somewhat depending upon whether the stoppage of the urine is immediate and complete or whether it is intermittent or partial, as it is with valves in the pelvis, with movable kidney, and with calculi. It is obvious that obstruction in the ureter leads to unilateral (Fig. 581), obstruction in the bladder or urethra to bilateral, hydronephrosis.

Experiments on animals[3] have shown that if the ureter is ligated there may be a very considerable hydronephrosis produced, with a primary distention of the pelvis of the kidney followed by enlargement of the collecting tubules and a growth of connective tissue in the substance of the kidney. The hydronephrotic process develops to a stage depending upon the back pressure on the glomeruli; when this reaches a certain point, the glomerulus ceases to secrete fluid and the kidney atrophies. This atrophy is probably also correlated with diminished blood supply to the kidney, for it may not occur if a good collateral circulation is estab-

[1] *Eisendrath, D. N.*, Surg., Gynec., and Obst., 1912, xv, 467.
[2] See, for a discussion of such cases, *Barney, J. D.*, Surg., Gynec., and Obst., 1912, xv, 290.
[3] See, for example, *Scott, G. D.*, Surg., Gynec., and Obst., 1912, xv, 296 (bibl.).

lished through the capsular vessels. Such sudden interruptions of urinary flow are not frequent in human beings, and when they do occur after operative ligature usually do not give rise to any extensive hydronephrosis. There may be a small amount of dilatation at first, chiefly of the pelvis, but later the kidney atrophies without symptoms, unless infection takes place. If the obstruction is released the organ shows astonishingly rapid restoration of functional power, even when the closure of the ureter has existed for a number of days or even weeks, but in order to regain function this release must take place before any extensive connective tissue growth has occurred in the kidney substance.

When, for any reason, the urinary flow is interfered with only partially or intermittently, the hydronephrosis is very much greater in extent than in complete closure, and the kidney substance may atrophy almost completely, so that the organ is turned into a large lobulated sac which may contain many liters of clear, bloody, brownish, or opalescent fluid. The thinned-out kidney is pale and firm on account of the new formation of connective tissue. The walls of the blood-vessels are thickened, the lining membrane may be smooth or covered with warty thickenings of epithelium or masses of fibrin and débris. Usually a few remnants of glomeruli and tubules can be found microscopically in the thin sac wall.

The reason for the more extensive hydronephrosis following partial or intermittent closure is that the pressure does not lead to early interference with the secreting power of the kidney, so that the glomeruli continue to furnish urine and the kidney tissue regenerates when the pressure is relieved; then when the flow is again interfered with fresh dilatation takes place; this long-continued repetition of the alternate process of regeneration and compression accounts for the large sacs which may form.

PERINEPHRITIC SUPPURATION.

The loose connective tissue about the kidney may become the seat of suppurative inflammation. This may follow mechanical injury or may be secondary to suppurative or other inflammatory processes, such as caries of the spine, empyema, pelvic cellulitis, puerperal parametritis, perityphlitis, and suppurative nephritis. It may be associated with acute infectious diseases in children. The suppuration may extend backward through the muscles; downward into the iliac fossa, the perineum, the bladder, the scrotum, or the vagina; forward into the peritoneal cavity or the colon; or upward through the diaphragm.

The kidney itself may be simply compressed by the abscess or may become involved in the suppurative process.

CYSTS IN THE KIDNEYS.

Cysts are formed in the kidneys during either intrauterine or extrauterine life.[1]

Congenital Cystic Kidneys are often striking objects. Either one or, more frequently, both kidneys may be greatly enlarged and converted into a mass of cysts (Fig. 582). The cysts are of various sizes and are

[1] For bibl., see *Berner*, Die Cystenniere, Jena, 1913.

separated from each other by fibrous septa or compressed kidney tissue. They contain a fluid which may be clear, yellow, and acid, holding in solution the urinary salts, or may be turbid and brown, and contain blood, uric-acid crystals, and cholesterin. The cysts are often lined with a single layer of flat, polygonal cells. Some of them seem to be formed by a dilatation of the tubules and of the capsules of the Malpighian bodies. As causes for such dilatations there may be found obliteration of the tubes in the papillæ, and stenosis of the pelvis, ureters, bladder,

FIG. 581.—HYDRONEPHROSIS.
From obstruction of ureter.

or urethra. Other congenital malformations, such as cortical adenomata, islands of cartilage, and pearly or squamous epithelium, are not infrequent in cystic kidneys, a fact which strengthens the view that the lesions have a developmental origin, as does the occurrence of even grosser defects in the genitourinary system and other organs. The most widely accepted attitude is that the whole lesion is due in many cases to lack of junction of the urinary tubules with the budding canals from the pelvis. As this failure of union may occur at different stages of development, various types and locations may be observed.

The surgical removal of a cystic kidney is usually followed by the death of the patient, for the amount of functional kidney tissue in the

other organ is apt to be too small to allow proper elimination of waste products, even though previous functional tests may have suggested good permeability.

Cysts of the Kidney in the Adult may be single and occur in otherwise normal organs. There may be one or more cysts filled with clear or colored serum or gelatinous material (Fig. 583). These cysts do not appear to interfere with the function of the kidneys.

In chronic diffuse nephritis, especially in the atrophic form, groups of tubes may be dilated. Apparently one or more of the larger tubes in the pyramids are obstructed, and this causes dilatation of a corresponding group of tubes. Such a dilatation may be moderate in size, or it

FIG. 582.—CONGENITAL CYSTIC KIDNEY.
Only very small portions of the kidney tissue remain, crowded between the cysts.

may form cysts visible to the naked eye. Very small cysts of Bowman's capsule may form, with atrophy of the vascular tuft.

Occasionally both kidneys are very much enlarged and converted into a mass of cysts containing clear or colored serum or gelatinous material. The nature of these cysts is uncertain; they may be congenital; and they are sometimes associated with similar cysts in the liver.[1]

Some six cases of dermoids of the kidney have been reported.[2]

[1] For a study of cystic kidney with extensive bibl., see *Ritchie*, Laboratory Reports, Royal Coll. of Phys., Edinburgh, vol. iv; also *Braunwarth, C.*, Virchows Arch., 1906, clxxxvi, 341 (bibl.).

[2] *Baldwin, J. F.*, Surg., Gynec. and Obst., 1915, xx, 219

FIG. 583.—SINGLE CYST OF THE KIDNEY.

FIG. 584.—CALCULUS IN THE PELVIS OF THE KIDNEY.

Small multiple cysts of the ureter, lined with flattened or cuboidal epithelium, are of occasional occurrence, and may be associated with similar cysts in the pelvis of the kidney. Such cysts in the ureter may be pedunculated.[1]

RENAL CALCULI.

In the kidneys of new-born children, from the first to the fourteenth day after birth, the large tubes of the pyramids often contain small brownish, rounded bodies composed of the urates of ammonium and sodium. Similar masses may also be present in the calyces and pelves. In still-born children these masses are usually absent. The carbonate and phosphate of lime, in the form of white linear masses, may be deposited in the tubes of the pyramids, in the kidneys of old persons and of those who have suffered from destructive diseases of the bones.

Urate of soda in the form of acicular crystals is deposited both in the tubes and in the stroma of the kidneys of gouty persons.

Concretions of the urinary salts are often formed in the pelves of the kidneys. They may remain there as rounded masses (Fig. 584), or they may attain a large size and be moulded into the shape of the pelvis and calyces. Smaller calculi may pass into the ureter and either become impacted there or pass through it into the bladder. The most common form of calculus is that composed of uric acid. But they may also be formed of uric acid with a shell of oxalate of lime, or of oxalate of lime alone, or of the phosphates, or of cystin.[2]

Fig. 585.—Small Adenoma of Kidney. Situated in the cortex.

The most serious result of the presence of these calculi is the occlusion of the ureters or the incitement of pyelonephritis.

TUMORS.[3]

Small **fibromata, lipomata, myomata,** and **angiomata** may occur in the kidney and, with the exception of the fibromata, are most common in the cortical portion. **Papilloma** may form in the mucous membrane of the pelvis. **Sarcoma** and **myxosarcoma,** often of large size, may develop in the kidney; these are frequently soft and vascular and are prone to hemorrhage. Primary sarcoma of the kidney is common in children. Secondary carcinoma and sarcoma are not rare.

[1] For a résumé of cysts of the ureter with bibl., see *Harris*, Am. Med., 1902, iii, 731.

[2] For a study of the composition of renal calculi, see *Ultzmann, R.*, Die Harnconcretionen des Menschen, Wien, 1882; *Fowler, H. A.*, Johns Hopkins Hosp. Rep., 1908, xiii, 507; *Kleinschmidt, O.*, Die Harnsteine, Berlin, 1911; *Kahn, M.*, Arch. Int. Med., 1913, xi, 92; *Rosenbloom, J.*, Jour. Am. Med. Assn., 1915, lxv, 161.

[3] For a general discussion of tumors of the kidney, see *Nuernberg, F.*, Frankfurt. Ztschr. f. Path. 1907, i, 433 (bibl.).

There often occur in childhood **mixed tumors** of the kidney which have a sarcomatous and adenomatous character or may contain mucous or elastic or striated muscle tissue, cartilage, and bone, with structures suggesting glomeruli.[1] In all probability these tumors are teratoid in nature and arise by the simultaneous segregation of nephrogenous and muscle tissue at a very early embryonic stage. A few much more complex tumors, with ectodermal and other structures, have been described, suggesting segregation at a still earlier stage.

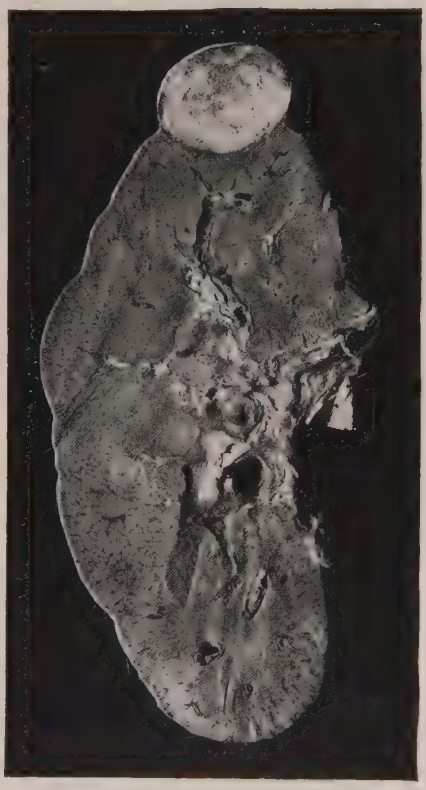


Fig. 586.—Adenoma of the Kidney. (Hypernephroma.)
A tumor of the kidney formed from aberrant adrenal tissue.

Adenoma is of frequent occurrence in the kidneys. It usually originates in the cortex and may be invisible to the naked eye (Fig. 585), or, in the form of a well-defined, circumscribed nodule (Fig. 586 and 587), it may invade the medulla or largely replace the kidney. The adenomata are usually light in color save when very vascular with hemorrhage, and may be separated from the kidney structure by a fibrous capsule. It is probable that many of these tumors are due to arrested development of the kidney parenchyma. Such tumors are not rare in children.[2]

There are two principal varieties of these tumors, the *papillary* and the *alveolar*, which are, however, closely related.

1. *Papillary Adenoma.*—There are cavities of different sizes, from the walls of which spring branching tufts covered with cylindrical or cuboidal epithelium (Fig. 588). These tufts nearly fill the cavities. Occasionally neoplasms of the type of adenoma form metastases at a distance, and hence they must be considered, despite their morphology, as carcinomata.[3]

2. *Alveolar Adenoma.*—There is a connective-tissue framework inclosing small round, oval, or tubular alveoli, lined or filled with cells (Fig. 589). The cells are usually large, either cylindrical, cuboidal, or

[1] For a study of the mixed tumors of the kidney, see *Wilms*, Die Mischgeschwülste der Niere, Leipzig, 1899; *Hedrén, G.*, Zieglers Beitr., 1907, xl, 1 (bibl.); *Buerger* and *Lautman*, Am. Jour. Surg., 1914, xxviii, 453.

[2] *Engelken, H.*, Zieglers Beitr., 1899, xxvi, 320 (bibl.); *Dunn, J. S.*, Jour. Path. and Bacteriol., 1913, xvii, 515.

[3] *Kretschmer, H. L.*, and *Moody, A. M.*, Surg., Gynec., and Obst., 1914, xix, 766.

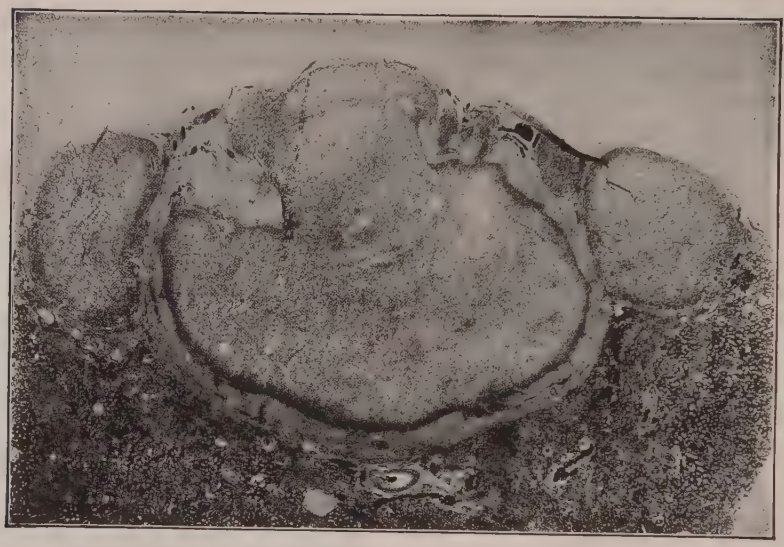


FIG. 587.—ADENOMA OF THE KIDNEY.
Showing encapsulation of the nodules.

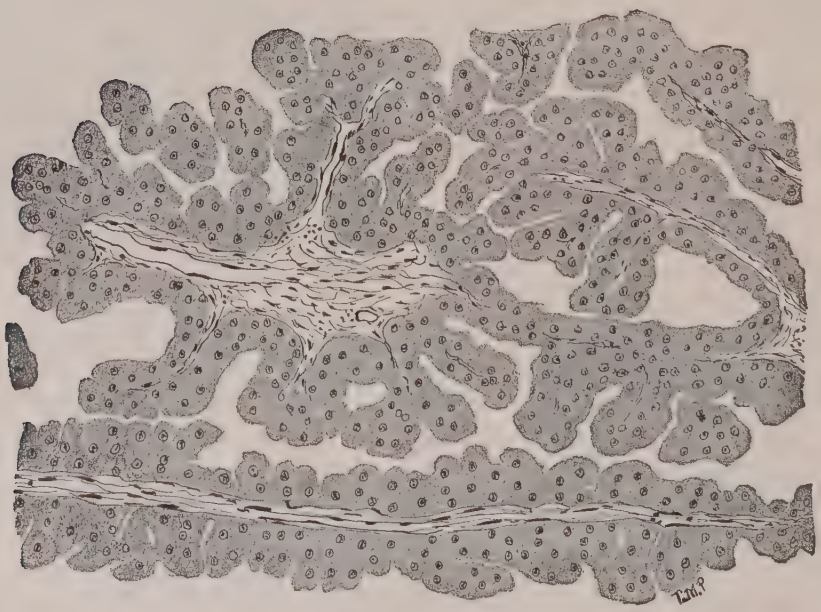


FIG. 588.—ADENOMA OF THE KIDNEY.
Papillary variety.

polyhedral, and may be pigmented or fatty in a manner similar to the cells of the adrenals.

Hypernephroma.—The most frequent type of kidney tumor is that long considered as arising from remnants of adrenal tissue. These tumors vary from those a few millimeters in diameter to large neoplasms occupying a considerable portion of the abdomen. The cut surface has the dull yellow color of the adrenal cortex. The microscopic appearance resembles that of the adrenal (Fig. 586 and 590). The cells are filled with fat globules and contain a large amount of glycogen. The interstitial tissue is small in amount and through it runs a fine capillary network. In the more malignant type, giant cells (Fig. 591) may be found, or the stroma may take on active growth and the tumor simulate a spindle-cell sarcoma. Recently[1] the view has been gaining ground that these growths are renal and not adrenal in origin, and it has been pointed out that in the undoubted adenomata cells may be found which resemble those of supposed adrenal origin. The problem needs further study for its solution. Owing to the high vascularity of the tumors, hemorrhages are very apt to occur in their substance, often leading to the formation of large hemorrhagic cysts. Intravascular growth is frequent and the tumor may invade the vena cava or even the heart,[2] or proceed to the pelvis of the kidney, in the latter instance calling early attention to its presence by the profuse hematuria which accompanies such extension. Metastasis is frequent, especially in the lungs and bone-marrow,[3] but the liver, intestine, retroperitoneal and other lymph-nodes, and even the skin may be the seat of numerous deposits.

A retrogression or quiescence of the primary tumor has been observed, lasting for years after operative removal of a bone-marrow metastasis in the tibia.

Primary **carcinoma** of the kidney is rare, adenoma being frequently mistaken for it.[4] The morphology may be adenocarcinomatous or medullary in type. Early invasion of the whole organ is usual and metastases in the opposite kidney are frequent. Squamous-cell tumors are derived from the mucous membrane of the pelvis.

Primary tumors of the renal pelvis are very rare; from this site they may metastasize and involve the ureter and bladder.[5]

PARASITES.

Echinococcus, in its ordinary form of mother and daughter cysts, is sometimes found in the kidney. The cysts may open into the pelvis of the kidney, into the pleura, or through the wall of the abdomen.

Cysticercus cellulosæ is of very rare occurrence. **Filaria bancrofti** is found in the arteries, veins, lymphatics, and stroma, and may pass

[1] *Grawitz, P.*, Virchows Arch., 1883, xciii, 39; *Stoerk, O.*, Zieglers Beitr., 1908, xliii, 393; *Sisson, W. R.*, Zieglers Beitr., 1910, xlix, 476; *Wilson* and *Willis*, Jour. Med. Research, 1911, N. S. xix, 73; *Ipsen, J.*, Zieglers Beitr., 1912, liv, 233; *Fraser, A.*, Surg., Gynec., and Obst., 1916, xxii, 645; *Glynn, E. E.*, Quart. Jour. Med., 1912, v, 157; *Dunn, J. S.*, Jour. Path. and Bacteriol., 1913, xvii, 515.

[2] *Jacobson, V. C.*, and *Goodpasture, E. W.*, Arch. Int. Med., 1918, xxii, 86 (bibl.).

[3] *Scudder*, Ann. Surg., 1906, xliv, 851.

[4] For a careful study of tumors and other growths in the kidney, see *Kelynack*, Renal Growths, 1898 (bibl.); also bibl. by *Busse, O.*, Virchows Arch., 1898, clvii, 346, 377. For a statistical study of malignant tumors of the kidney in children, see *Oshima, T.*, Wien. klin. Wchnschr., 1907, xx, 93.

[5] *Lower, W. E.*, Surg., Gynec., and Obst., 1914, xviii, 151 (bibl.).

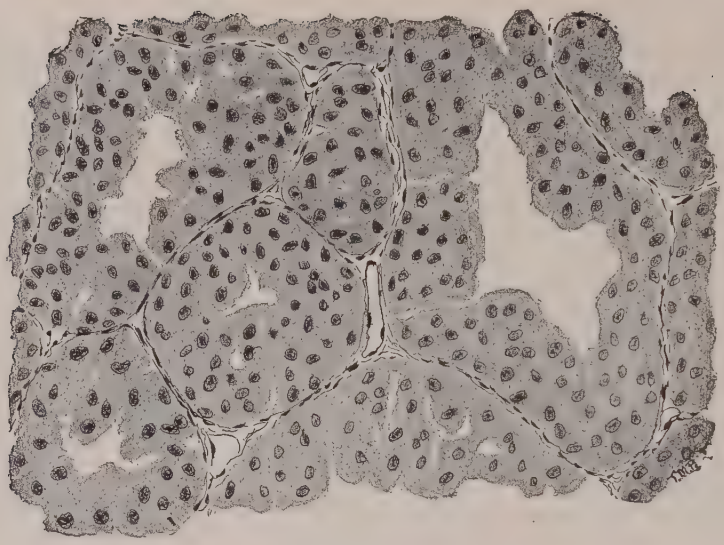


FIG. 589.—ADENOMA OF THE KIDNEY.
Alveolar variety.

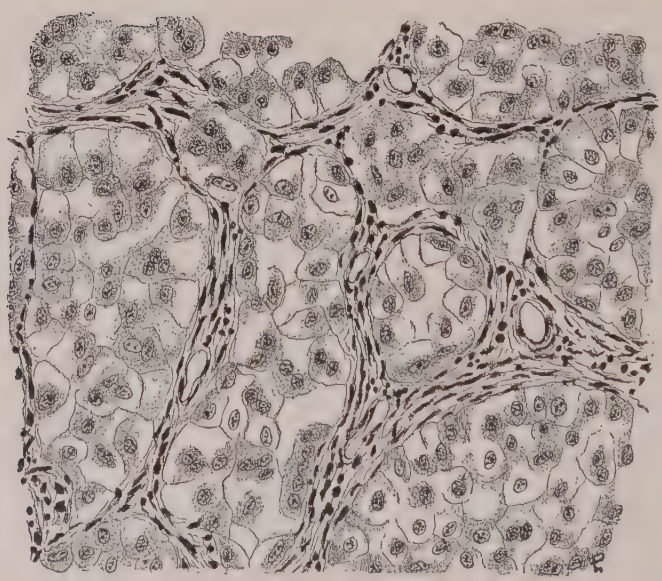


FIG. 590.—HYPERNEPHROMA.
The cells filling the alveoli are in part transparent, resembling those of the adrenal.

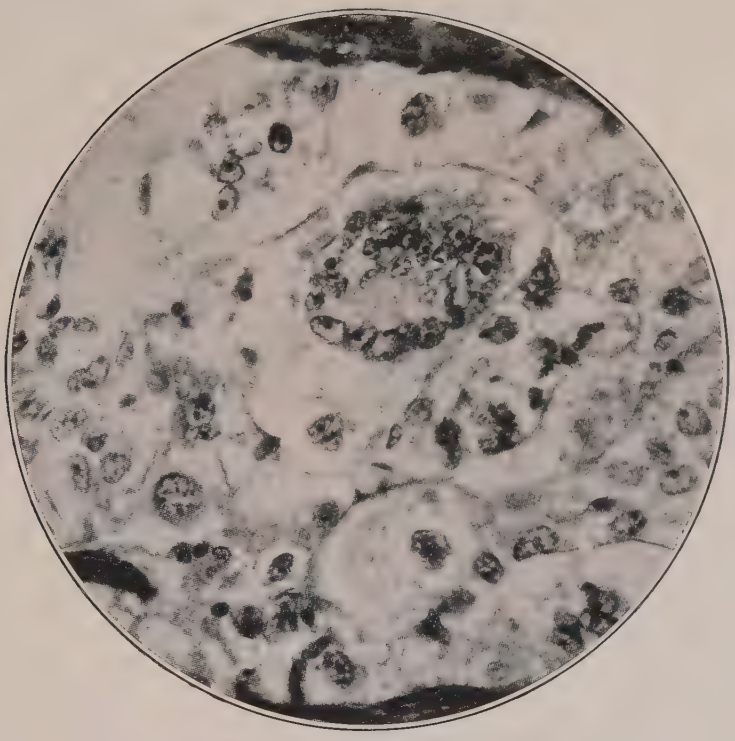


FIG. 591.—HYPERNEPHROMA.
Metastasis in lymph-node of arm. Atypical form with multinucleated cells.

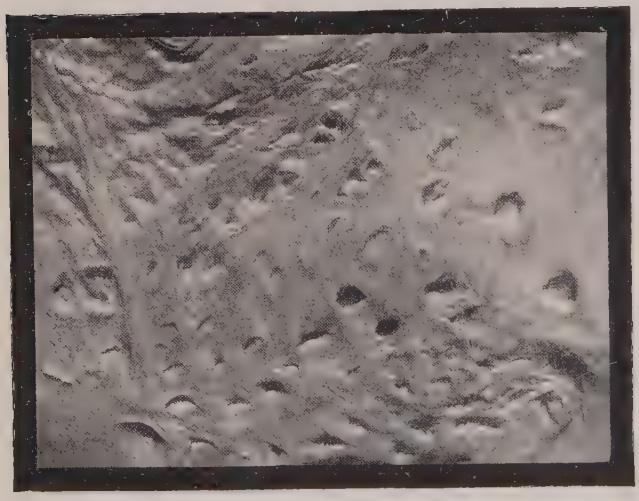


FIG. 592.—DIVERTICULA OF THE BLADDER.

into the urine. **Eustrongylus gigas** has been found several times in the pelvis of the kidney.

The Urinary Bladder.

Malformations.

ABSENCE OF THE BLADDER is of rare occurrence. The bladder may be very small, the urine passing almost directly into the urethra. The bladder may be separated into an upper and a lower portion by a circular constriction. It may be completely divided by a vertical septum into two lateral portions. Diverticula of the wall of the bladder are sometimes found in newborn children. Partial or complete closure of the neck of the bladder may occur. This may lead to hydronephrosis, or the urine may be discharged through the open urachus.

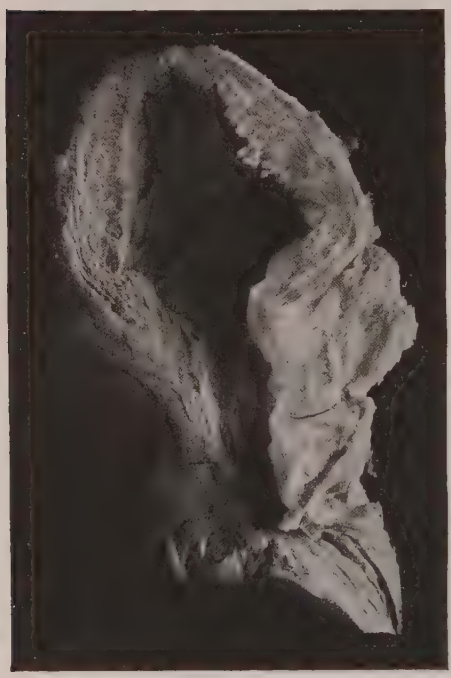


FIG. 593.—HYPERTROPHY OF THE WALL OF THE BLADDER.

EXTROVERSION of the bladder is one of the most frequent malformations, and may occur in either sex. It presents several varieties:[1]

1. The umbilicus may be lower down than usual, the pubic bones not united at the symphysis, and the pelvis wider and shallower than it should be. Between the umbilicus and pubes the abdominal wall may be wanting. In its place may be a projecting, ovoid mass of mucous membrane, in which may be seen the openings of the ureters. The penis is usually rudimentary; the urethra an open fissure (epispadias); the clitoris may be separated into two parts. The ureters usually open normally; sometimes their openings are displaced or are multiple. They may be dilated.

2. There may be a fissure in the abdominal wall, filled up by the perfectly formed bladder.

3. The umbilicus may be well formed, and there may be a portion of abdominal wall between it and the extrophied bladder.

4. The external genitals and urethra may be well formed, and the symphysis pubis united, while only the bladder is fissured.

5. The genitals, urethra, and symphysis may be well formed, the bladder closed except at the upper part of its anterior wall. The bladder may be entirely or in part inverted and pushed through the opening in the abdominal wall.

The URACHUS normally remains as a small fibrous cord, 12 cm. long. and 1.5 mm. in diameter, extending under the peritoneum from the apex of the bladder to the umbilicus. It is not patent after birth, except that occasionally a very small canal lined with epithelium and from 5 to 7 cm. long remains. This may or may not open into the bladder. Fluid may collect in such a patent urachus and give rise to single or multiple cysts, which occasionally reach a very large size. The cysts are lined with epithelium; they may suppurate or calculi may form in their lumina. In rare

[1] *Mayo, C. H.*, Jour. Am. Med. Assn., 1917, lxix, 2079; *Enderlen*, Samml. klin. Vortr. (Volkmann), 1908, No. 472.)

instances the urachus may remain patent throughout its entire length, and the patient may pass urine simultaneously from the urethra and the umbilicus. If the normal exit of urine is obstructed, the remnant of the urachal tube may dilate and an acquired urinary fistula develop at the umbilicus.

Carcinomata and *sarcomata* have been described as originating in the urachus, and two cases of *tuberculosis* are on record.[1]

Changes in Size and Position.

Dilatation.—This may be *general* or *partial*, leading to the formation of diverticula.

General dilatation of the bladder is produced by the accumulation of urine in consequence of some mechanical obstacle to its escape, or of paralysis of the muscular walls of the organ. The dilatation is usually uniform and may be very great, so that the bladder may reach to the umbilicus. If the walls of the bladder are paralyzed, or the obstruction occurs suddenly or is complete, the wall of the bladder is thinned. When an incomplete obstruction exists for some time the walls of the bladder are apt to hypertrophy, so that, although the bladder is larger than normal, the walls may not only be of the usual thickness, but even very much thicker. In the fetus dilatation of the bladder may reach such a size as to interfere with delivery.

The retained urine in dilated bladders is liable to decomposition, from the presence of bacteria, and this may lead to inflammation or gangrene of the mucous membrane.

Diverticula of the bladder may be produced by the pouching out of circumscribed portions of the wall of the organ, the wall of the pouch containing all the layers of the bladder wall. More frequently, however, they are produced by a protrusion of the mucous membrane between hypertrophied bundles of muscle fiber. They may be very small (Fig. 592), or they may be as large as a child's head. They may communicate with the bladder by a large or small opening. The decomposition of stagnant urine in diverticula is apt to induce inflammation with ultimate formation of adhesions. Calculi may be formed in them or may slip into them from the bladder. Mechanical obstruction to the outflow of urine is the usual cause, urethral stricture, phimosis, and prostatic hypertrophy being the most frequent exciting agents; but simple trauma of the bladder region may be followed by diverticula.[2]

Hypertrophy of the muscular coat of the bladder is usually due to mechanical obstructions to the outflow of urine, such as stricture of the urethra, enlarged prostate, calculi, new growths, etc. The muscular coat is thickened uniformly or assumes a trabeculated appearance (Fig. 593). The organ retains its normal capacity, or is dilated, or becomes smaller. The mucous membrane is frequently the seat of chronic or acute inflammation. Dilatation of the ureters and hydronephrosis frequently accompany this condition.

Herniæ of a portion of the bladder wall sometimes accompany intestinal herniæ through the inguinal and crural canals and the foramen ovale. The changes in position of the bladder produced by displacements of the vagina and uterus will be mentioned with the lesions of those organs.

In the female, after injury of the perineal floor following delivery, the base of the bladder may press downward, causing protrusion of the vaginal wall (*vaginal cystocele*); or there may be inversion and prolapse of the bladder through the dilated urethra.

WOUNDS—RUPTURE—PERFORATION.

Penetrating *wounds* of the bladder may permit escape of urine into the abdominal cavity, or infiltration into the surrounding connective tissue, or permanent fistulæ. Such wounds are always serious and frequently fatal, owing chiefly to the severe and often gangrenous inflammation which decomposing urine sets up in the connective tissue, or to the peritonitis induced by the same cause.

[1] For further details and bibl., see *Cullen*, The Umbilicus and Its Diseases, Philadelphia, 1916.
[2] *Thomas, G. J.*, Surg., Gynec., and Obst., 1916, xxiii, 378.

Rupture of the bladder may be produced by severe blows and falls when the bladder contains urine. More rarely rupture takes place from overdistention, especially in tabes or transverse lesions of the spinal cord. Death may occur from rupture of the bladder with escape of urine into the peritoneal cavity, without evidences of peritonitis.

Perforations of the bladder may be due to ulceration, either simple or cancerous, to gangrene, to abscesses from without, and to cancerous ulceration from the adjoining organs. Fractures of the pelv c bones may be accompanied by laceration of the bladder. Perforations of the bladder may lead to the establishment of fistulæ, communicating with the rectum, vagina, or uterus, or opening externally.

DISTURBANCES OF CIRCULATION.

Hyperemia.—Aside from active hyperemia of the mucous membrane in acute inflammation, the bladder is not infrequently the seat of chronic congestion from obstruction to the venous circulation. Under these conditions there may be chronic catarrhal inflammation, or a marked dilatation of the veins (vesical hemorrhoids), which may give rise to hemorrhage or to obstruction of the opening of the ureters.

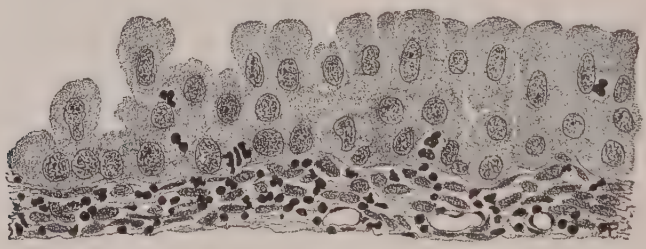


Fig. 594.—Acute Catarrhal Cystitis.
There are exfoliation of epithelium and emigration of leucocytes from the submucosa.

Hemorrhage.—Extensive hemorrhages into the bladder are commonly due to injury or to the presence of calculi, tumors, or filariasis. In this condition the urine is usually also clouded with finely divided fat—*chyluria.* Small hemorrhages into the substance of the mucous membrane may accompany inflammation, the hemorrhagic diathesis, scurvy, purpura, smallpox, etc. Small amounts of blood are not infrequently passed in the urine in tuberculosis or syphilis of the bladder. If the hemorrhage is considerable and occurs rapidly in an empty bladder, a clot is apt to form; but when the blood mixes with urine as it is extravasated, it more commonly remains liquid and is discharged as a reddish brown fluid.

INFLAMMATION. (Cystitis.)

Acute Catarrhal and Exudative Cystitis.—This may be incited by the presence of urine which has decomposed under the influence of bacteria; by cantharides or other drugs; by the presence of foreign bodies and calculi; it may be due to an extension of gonorrheal urethritis or vaginitis;

or it may occur with acute general infectious diseases. The mucous membrane is swollen and congested, although these alterations may not be very evident after death. There may be ecchymosis; the epithelium is granular, and may proliferate and peel off. Leucocytes may infiltrate the submucosa and pass out between the epithelial cells (Fig. 594). Mixed with the urine there may be shreds of mucus, pus cells, epithelial cells of various shapes, usually more or less swollen and granular, or fragments of such cells; red blood-cells, bacteria, and various urinary crystals; abscesses may form in the mucous membrane; or there may be phlegmonous inflammation in the submucosa and muscularis of the bladder with formation of abscesses. Thus perforations and fistulæ may occur. Resolution may take place after acute catarrhal and exudative cystitis, but the inflammation very frequently assumes a chronic character.

Chronic Cystitis.—In this form the mucous membrane may be swollen,

Fig. 595.—Hyperplasia of the Bladder Epithelium.
The hyperplastic epithelium is transparent and, dipping into the submucosa, forms gland-like structures.

succulent, grayish, or mottled with spots of congestion or extravasation, and covered with a layer of mucus and pus. Microscopically the membrane may be more or less infiltrated with pus cells, and pus may be constantly produced and thrown off into the urine. Later the mucous membrane may become thickened either diffusely or in the form of tufts or polypi. In some cases it becomes atrophied. Owing to decomposition of hemoglobin in the extravasated blood the mucosa may become pigmented, brown, or slate-colored. The mucous membrane frequently becomes eroded, especially on the most elevated portions, or deep ulcerations may occur. The muscular coats may become paralyzed and the bladder dilated; or the submucosa or the muscularis, or both, may become hypertrophied. The mucous membrane may become encrusted with urinary salts.

In another class of cases the inflammation assumes a necrotic charac-

ter. Larger and smaller patches of the mucosa die, become brown or gray in color, loosen or peel off and become mixed with the urine and exudations. The gangrenous process may extend to all the coats of the bladder, so that perforation and fatal peritonitis may occur. The gangrenous form of cystitis is more apt to occur in paralytics.

In still another class of cases the inflammation is suppurative. The submucosa, the intermuscular connective tissue, and the adjacent parts become infiltrated with pus, either diffusely or in the form of larger and smaller abscesses, which may open externally or internally, forming deep ulcers. In all these cases the inflammation may extend to the ureters and kidneys; it may skip the ureters and involve the kidneys.

The small nodules of lymphoid tissue in the mucous membrane of the bladder, especially near the neck, may become enlarged and prominent in cystitis, and may then be mistaken for miliary tubercles (nodular cystitis).

Hyperplasia of the epithelium of the bladder sometimes occurs in chronic cystitis and under other conditions. This may be diffuse or circumscribed and the epithelium may assume a squamous character. Thus masses of transparent epidermis-like cells may lie between papillary projections of the submucosa, forming structures which resemble glands

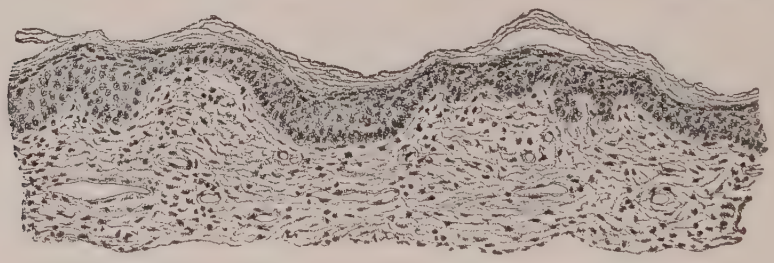


Fig. 596.—Hyperplasia of the Bladder Epithelium.
The epithelium has assumed the squamous type and is exfoliating.

(see Fig. 595), or layers of flattened epithelium may cover or peel from the surface (see Fig. 596).[1]

The hyperplasia and subsequent softening of the epithelium in the deep crypts (Fig. 595) may lead to the formation on the surface of minute cysts filled with clear yellow or brownish fluid (*cystitis cystica*).[2] The lesion in the bladder is most usually about the trigone; it may involve the rest of the urinary tract.

A few cases have been described in which scattered over the mucous membrane of the bladder are small thickened areas, from two to fifteen millimeters in diameter, usually surrounded by a hyperemic zone, and frequently ulcerated. These areas of chronic inflammatory thickening are formed by hyperplasia of the connective tissue with small-cell infiltration and by peculiar large cells which appear to be phagocytes con-

[1] For a study of regeneration in the mucous membrane of the bladder, see *Lasio, G.*, Virchows Arch., 1904, clxxviii, 65.

[2] For bibl. of cystitis cystica, see *Stoerk, O.*, Zieglers Beitr., 1911, l, 361.

taining red blood-cells, fragments of other cells, bacteria, etc. The nature of this lesion is not yet clear. It has been called *malakoplakia* and *cystite en plaque*.[1]

Membranous Cystitis.—In connection with any of the above lesions the mucous membrane of the bladder may be covered, in patches or sometimes over a considerable portion of its surface, with a layer of fibrin, either granular or fibrillar, inclosing pus and epithelial cells and bacteria. The mucosa may be infiltrated with fibrin.

This form of inflammation may occur in connection with severe infectious diseases—measles, diphtheria, scarlatina, typhoid fever; in connection with similar inflammation of the external genitals; in puerperal fever and noma; and sometimes in the presence of foreign bodies. It rarely occurs independently. In severe types, a more or less complete cast of the bladder wall may be passed from the urethra.

In the so-called **emphysematous cystitis,** due to the presence of Bacillus aërogenes capsulatus, larger and smaller gas blebs may be present in the mucosa and underlying tissue.[2]

The most common microorganisms which act as excitants of acute catarrhal and exudative cystitis are Bacillus coli communis, Streptococcus pyogenes, and Staphylococcus pyogenes, the gonococcus and typhoid bacillus,[3] Bacillus proteus, and Bacillus aërogenes capsulatus. Many other forms are of occasional occurrence.[4]

Tuberculous Cystitis.—There may at first be miliary tubercles formed in the submucosa. These are often about the ureteral openings if the kidney is the source of the infection. By the coalescence of these and the degeneration of tissue about them, ulcers are formed, and it is most frequently in the ulcerative stage that the lesion is seen. The ulcers, which may be large or small, are usually most abundant at the base of the organ. Their edges may be cheesy, and miliary tubercles in greater or smaller numbers are usually found in the mucosa about them. Not infrequently large shreds of tissue are loosened and cast off. The mucosa about the ulcers is apt to be infiltrated with small spheroidal cells. Tubercle bacilli are present in many of the tubercles and in the edges and base of the ulcers, and may be found in the urine. Catarrhal inflammation is a very constant accompaniment of this lesion. Tuberculous cystitis may occur in connection with tuberculous inflammation of the lungs and intestines, or of the kidney, uterus, prostate, etc. In the early stages, the urine remains clear and acid; later secondary infections are usual, and the urine then contains much pus and mucus.

Syphilis.—In secondary syphilis, lesions of the same type as those occurring on the skin may exist in the bladder, giving rise to symptoms of cystitis, but without marked changes in the urine. A little pus or blood may be found in severe lesions. In tertiary syphilis, gummatous

[1] For a description and discussion of this lesion, see *von Hansemann*, Virchows Arch., 1903, clxxiii, 302; and *Landsteiner* and *Stoerk*, Zieglers Beitr., 1904, xxxvi, 131.

[2] See, for bibl., *Kedrowsky, W. J.*, Centralbl. f. allg. Path., 1898, ix, 817; *Ruppaner, E.*, Frankfurt. Ztschr. f. Path., 1908, ii, 343.

[3] See *Curschmann, H.*, München. med. Wchnschr., 1900, xlvii, 1449.

[4] For a study of bacteria of the urinary passages, see *Faltin*, Centralbl. f. d. Krankh. d. Harn- u. Sex.-Org., 1902, xiii, 130.

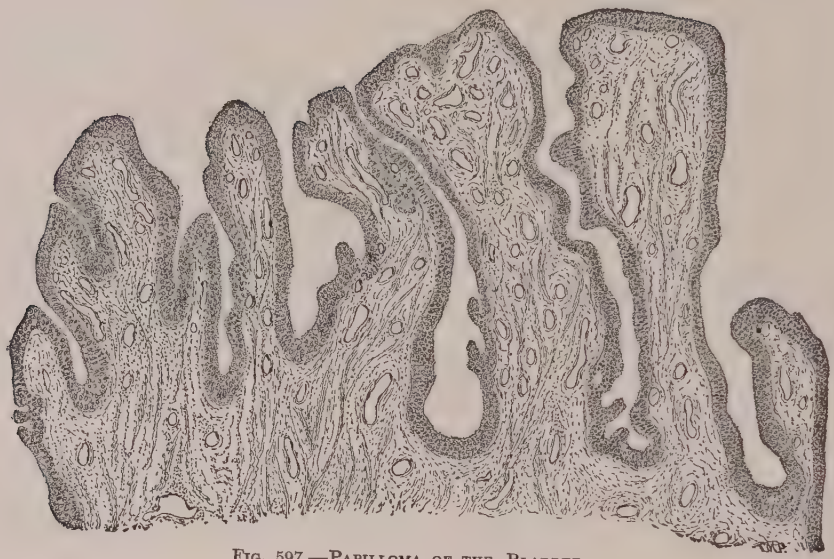


Fig. 597.—Papilloma of the Bladder.

Fig. 598.—Carcinoma of the Bladder.

or papillomatous lesions may develop in the bladder wall. Pain and hematuria are the most frequent symptoms.[1]

TUMORS.

Small nodular **fibromata** and **adenomata** may form in the submucosa. **Fibromyxomata, myxosarcomata, angiomata,** and **complex tumors** have been described. The last, which may contain bone, cartilage, striated muscle, and glandular structures must be due to congenital displacements of multipotent tissues.[2]

Aside from the polypoid thickenings of the mucosa occurring in chronic cystitis, soft vascular **papillomata** are of frequent occurrence. These tumors vary in size from that of a pea to that of a pigeon's egg or

Fig. 599.—Papillary Carcinoma of the Bladder.

larger. They consist of a fibrous, often very vascular stroma, and are covered on the surface with numerous small, closely set, villous projections, over which are irregular layers of elongated or cylindrical cells (Fig. 597). These tumors are very liable to bleed, are often accompanied by vesical catarrh, and may be covered by a precipitate of urinary salts. The epithelium is liable to peel off from the surface of the villi and appear in the urine. A number of examples have been reported in workers with aniline products.[3]

Sarcoma of the bladder has been described, but is rare.[4]

[1] For details and bibl., see *Fowler, H. A.*, Jour. Am. Med. Assn., 1917, lxix, 1399.

[2] *Fischer*, Arb. a. d. Path. Inst. z. Tübingen, 1908, i, 6; *Stumpf, R.*, Zieglers Beitr., 1911, 1, 171.

[3] *Nassauer, M.*, Frankfurter Ztschr. f. Path., 1919–20, xxii, 353; see, also, review in Medical Science, 1921, iii, 316.

[4] *Wilder, J. A.*, Am. Jour. Med. Sc., 1905, cxxix, 63.

Carcinoma.—Carcinoma of the bladder is often secondary, and is then due, not to metastasis, but to an extension of the growth from neighboring parts, as the uterus, vagina, prostate or rectum. Invasion by neoplasms of the kidney occurs either through the ureteral lymph-channels or by direct implantation of particles passing into the bladder in the urinary stream. Melanosarcomata involve the mucous membrane through the blood-stream. Vesical fistulæ not infrequently follow sloughing of the tumor.

Primary carcinoma of the bladder may occur:

1. As a diffuse *scirrhous infiltration* of the entire wall of the bladder, usually with ulcerations of its inner surface.

2. As a *circumscribed nodule* (Fig. 598) which grows inward and out-

Fig. 600.—Vesical Calculus.
Showing lamellations indicating successive depositions of different texture and composition.

ward, ulcerating on its inner surface, and sometimes producing perforations.

3. As a *villous* or *papillomatous growth.* The tumor grows from one or more points of the inner surface of the bladder. It is formed of tubular follicles lined with epithelium (Fig. 599), while on its surface are tufts covered with cylindrical epithelium The new growth may involve the entire thickness of the wall of the bladder.

4. A few cases of carcinoma have been described in which the stroma contained a varying quantity of smooth muscle tissue.[1]

Cysts.—*Dermoid cysts* of the wall of the bladder have been described, but are rare.[2] Small cysts with serous contents sometimes occur in the

[1] For study of carcinoma of the ureter, see *Metcalf* and *Safford*, Am. Jour. Med. Sc., 1905, cxxix, 50.
[2] See case by *Block* and *Hall*, Am. Jour. Med. Sc., 1905, cxxix, 651.

mucous membrane; a part of them, at least, are believed to be due to faulty embryonal development. *Echinococcus cysts* may form in the bladder wall or rupture into the lumen with the discharge of their contents through the urethra.

PARASITES, FOREIGN BODIES, AND CALCULI.

Among the animal parasites occasionally found in the bladder may be mentioned **Echinococcus, Schistosoma hæmatobium, Filaria bancrofti, Ascaris,** and **Oxyuris.**

A great variety of foreign bodies may be found in the bladder, particularly in the female. If their stay is long they are apt to become encrusted with urinary salts.

Calculi.

Vesical calculi may occur singly or in great numbers, and vary greatly in size, ranging from small, sand-like particles up to masses four or five inches in diameter; but the usual range is from the size of a pea to that of a hen's egg. They are usually oval, spheroidal, or elongated; or, when several are present, they are apt to be faceted. The surface may be smooth or rough. They are usually more or less distinctly lamellated, and are frequently formed around a central body called a nucleus, which may be formed either of urinary salts or of some foreign body. They are rarely composed of a single substance. Their most common constituents are *phosphates, uric acid* and *urates,* and *calcium oxalate,* or various combinations of these.

Uric-acid Calculi.—These are a frequent type of vesical calculi. In the form of small brownish red, crystalline aggregations they may be passed as "gravel." The larger uric-acid calculi are not commonly of very great size, are frequently finely nodulated on the surface, but may be smooth. The color varies from light yellow to dark reddish brown; they are usually dense and lamellated.

Calculi Formed of Urates.—Calculi composed of pure urates are rare, these salts being more commonly combined with uric acid and the phosphates to form the complex calculi. Sodium urate, in the form of small spined, more or less globular crystalline masses, forms one of the varieties of "gravel." Ammonium urate is the chief component of the larger stones.

Phosphatic Calculi.—Pure *calcium-phosphate* calculi, though rare, are found as whitish, usually smooth, and small lamellated concretions.

Mixed or Triple Phosphate calculi are common, and frequently attain large size. These calculi are sometimes pure, but the deposit is more frequently associated with other salts, either as encrusting or intercalated lamellæ. Triple-phosphate calculi are usually rough on the surface, of grayish white color, lamellated, and frequently very friable (Fig. 600).

Calcium-carbonate Calculi.—Small gray or white, hard, and usually smooth calculi of pure calcium carbonate occur rarely. Calcium carbonate is sometimes passed as gravel in the form of minute spheroidal bodies, either singly or in clusters.

Calcium-oxalate Calculi (*mulberry calculi*) are comparatively common, either pure or in combination with uric acid or the phosphates. Calcium oxalate may occur in the form of very small, hard, smooth concretions, or as larger, heavy, hard, finely or coarsely nodulated brown or blackish lamellated masses. The nucleus or some of the lamellæ, or both, are often composed of uric acid.

Cystin Calculi are usually ovoidal in shape, of waxy consistence, of clear or brownish or greenish yellow color, with mammillated surface and crystalline fracture. Cystin may be associated in a variety of ways with other calculi.

Xanthin Calculi, which are very rare, are usually of moderate size, smooth, of a cinnamon or cinnabar-red color, lamellated, and oval or flattened in shape.

Solid masses of fibrin and blood[1] or bacteria[2] sometimes occur in the kidney pelvis

[1] *Schmidt, M. B.*, Centralbl. f. allg. Path., 1912, xxiii, 865.

[2] For description of bacterial calculi in kidney, see *Neumann, A.*, Deutsch. med. Wchnschr., 1911, xxxvii, 1473.

or in the bladder, and may exist as independent structures, or form nuclei for the deposit of urinary salts.

For a detailed account of calculi, the conditions under which they form, modes of analysis, etc., we refer to special works on this subject.

The Urethra.

Malformations.

Some of the malformations of the urethra are described with those of the penis.

The urethra may be impervious or may open at the root of the penis. More commonly there is partial obliteration or stricture of some part of the canal. The entire urethra may be dilated into a sac.

There may be a canal on the dorsum of the penis, formed by the fusion of the spermatic cords, and opening in the glans above the urethra.

There may be two or more openings of the urethra. The canal may be misplaced so as to open in the inguinal region.

A number of cases have been reported in which a valve in the urethra has led to hypertrophy of the bladder, dilatation of the ureters, and hydronephrosis. Diverticula may occur in any portion of the urethra. They have been supposed to be due either to action of the valves just described, or to the congenital lack of closure of the genital furrow.[1]

Owing to its narrowness, greater length, and peculiar connections with the internal generative organs, the male urethra is much more liable to disease than the female.

Fig. 601.—Stricture of the Male Urethra.

Changes in Size and Position.

Dilatation of the urethra may be produced by strictures, or by calculi or other bodies fixed in its lumen. The dilatations are fusiform or sacculated in shape, and may reach the size of an orange or be even larger.

Strictures of the urethra are usually due to inflammation of its walls.

The stricture may be *temporary*, and due to a diffuse inflammatory swelling of the mucous membrane, or to the raising of the relaxed membrane into a fold or pocket.

Permanent strictures are produced by structural changes in the walls of the urethra.

1. The mucous membrane and submucous tissue become thickened in inflammation or as the result of injury and the new-formed fibrous tissue which contracts and narrows the canal.

2. Ulceration of the mucous membrane leaves cicatricial tissue, which contracts, and also produces adhesions and bands of fibrous tissue (Fig. 601).

3. There is fibrous induration of the corpus spongiosum and consequent constriction of the urethra.

The most frequent position of strictures is at the junction of the membranous and

[1] For further details and bibl., see *Englander, S.*, Jour. Am. Med. Assn., 1917, lxviii, 351.

spongy portions of the urethra, or close to this point. They also occur at the fossa navicularis and meatus, but more frequently in the prostatic portion. There may be one stricture or several. The consequences of stricture are dilatation of the urethra, the bladder, and the ureters, and hydronephrosis; inflammation and ulceration of the urethra behind the stricture, with perforation, infiltration of urine, or the formation of fistulæ.

The urethra may also be obstructed by folds of the mucous membrane; by muscular valves at the neck of the bladder; by wounds; by polypi and swollen glands; by new growths; by changes in the prostate and perineum; by calculi, mucus, blood, and echinococci coming from the bladder; by foreign bodies introduced from without.

Prolapse and inversion of the mucous membrane occur occasionally in young girls and women. There is a bluish-red swelling (*urethral caruncle*), from the size of a pea to that of a walnut, at the meatus. In the male, invagination of the mucous membrane of the urethra has been seen after injuries of the perineum.

INJURIES—PERFORATION—HEMORRHAGES.

Wounds of the urethra are produced in many ways, but most commonly by catheters and bougies. The wounds may cicatrize, or there may be infiltration of urine or the formation of fistulæ or false passages.

Ruptures of the urethra are produced by severe contusions and by fracture of the pelvic bones. Extravasations of blood and urine, and gangrenous inflammation of the surrounding soft parts, are the ordinary results. Urethral varices in the female may lead to hemorrhage.

Ulceration and *perforation* of the urethra may lead to the formation of fistulæ, which open in various directions through the skin.

INFLAMMATION. (Urethritis.)

Catarrhal Urethritis may be due to the action of chemical irritants, and to the extension to the urethra of inflammation from other parts; but its most frequent excitant is the gonococcus. In its acute form it involves either a portion or the whole of the urethra. The mucous membrane is red, swollen, and covered with mucopus. The epithelium may be loosened or exfoliated; pus cells are present in the submucosa between the epithelial cells. The gonococcus is present usually in considerable numbers in the exudate, both free and in the pus cells. It may penetrate between the epithelial cells.

Resolution may follow acute gonorrheal urethritis. But the condition may become chronic and then is often confined to the posterior portions of the urethra. Here the gonococcus may persist for a long time and may be mingled with the exudate, which is now less purulent and consists very largely of mucus which in thread-like forms may be passed with the urine.

Chronic Inflammation of the urethra may exist for a long time with the production of a mucopurulent exudation, but without the occurrence of marked structural lesions. In other cases it leads to ulceration, to fibrous induration of the wall of the canal (see Fig. 601), to induration and swelling of the mucous follicles, to polypoid thickenings of the mucous membrane.

The inflammation may extend to the fibrous wall of the urethra, the

corpora spongiosa and cavernosa. This may result in the formation of new connective tissue or of abscesses, especially near the fossa navicularis. There may be involvement of the bladder, the glands of Cowper, the prostate, the spermatic cord, and the testicles. The inguinal nodes also may be swollen and inflamed, and the lymphatic vessels on the dorsum of the penis may be involved in the same process.

Membranous Inflammation is sometimes seen, especially in children. Fibrinous casts of a small or large portion of the canal may be formed.

Tuberculous Inflammation occurs in the mucous membrane of the urethra in connection with tuberculous inflammation of the bladder, prostate, or testicles, but is rare.

Syphilitic Ulcers may be situated at the meatus or as far back as the fossa navicularis. They are apt to produce strictures.

TUMORS.

Aside from the polypoid outgrowths from the mucous membrane of the urethra as the result of chronic inflammation or of stricture, **fibrous polyps** may occur congenitally; polyps containing glandular structures or cysts are rarely seen.[1] **Carcinoma** may occur as a result of local extension from adjacent organs or metastasis from the bladder and with extreme rarity as a primary growth.[2]

Cysts may occur in the membrane as a result of the dilatation of the mucous glands. Circumscribed masses of dilated veins occasionally occur in the urethra, forming the so-called **urethral hemorrhoids.**

The sinus pocularis may be dilated in children by the retention of its secretion, so as to form a mass which may obstruct the exit of urine and lead to hypertrophy of the bladder and dilatation of the ureters.

[1] *Fluss, K.*, Wien. klin. Wchnschr., 1907, xx, 1225.

[2] *Kaufmann, C.*, Deutsch. Chir., 1886, Lief. 50 A (very complete bibl.); and *Preiswerk*, Ztschr. f. Urol., 1907, i, 273.

CHAPTER X.

THE REPRODUCTIVE ORGANS OF THE FEMALE.[1]

The Vulva.

Malformations.[2]

The external genitals may be entirely absent or imperfectly developed; this occurs chiefly in fetuses otherwise so deformed that they are not viable. The fissure between the labia may be unformed, or the labia may have grown together, with or without obstruction of the urethra. The clitoris and nymphæ may be abnormally large, or the nymphæ may be increased in number. The clitoris may be abnormally long; at the same time the vagina may be narrow; the uterus small and undeveloped or malformed, the ovaries small and sometimes situated in the labia; the mammæ small; and the body of a masculine character. These are the characteristics of infantilism. The clitoris may be perforated by the urethra or may be cleft and apparently double.

The hymen is subject to various anomalies: it may be entirely absent; the opening may be very large or in an unusual place; there may be several openings; the free edge may be beset with papillary projections; or there may be no opening at all (imperforate hymen).

HEMORRHAGE, HYPEREMIA, ETC.

Hemorrhage may take place from wounds or ulcers of the vulva, but the most important form is that which takes place in the connective tissue of the labia majora; this may occur during labor or may result from external injury. One of the labia may be much swollen and distended by the extravasated blood. The accumulation of blood may produce sufficient pressure to rupture the overlying parts so that profuse external hemorrhage results; or the blood may be gradually absorbed, or may decompose with suppuration or gangrene of the surrounding tissue.

Varicose Veins in the labia are not infrequent, but are most common during pregnancy. Edema of the labia majora may occur in pregnancy or in labor. It frequently accompanies disturbances of the venous circulation, as in certain heart and lung diseases; or it may result from systemic conditions, as chronic diffuse nephritis or wasting diseases, or from local causes, as a result of thrombosis[3] or other disturbances of cir-

[1] The most important source of information on the pathology of the female generative organs is the Handbuch d. Gynakologie, edited by *J. Veit*, 2d ed., Wiesbaden, 1908. Much recent knowledge is given in the well illustrated Handbuch d. gesamten Frauenheilkunde, edited by *W. Liepmann*, Leipzig, 1914. Of the recent works in English the most valuable is the three volume System of Gynaecology, edited by *Eden* and *Lockyer*, London, 1917. Useful information on the diagnosis of gynecological lesions, though somewhat out of date, is contained in *Gebhard, C.*, Pathologische Anatomie d. weiblichen Sexualorgane, Leipzig, 1899. A recent and most valuable text is *Frank, R. T.*, Gynecological and Obstetrical Pathology, New York, 1922.

[2] For full details of the embryology and malformations of the female generative organs, see *Felix, W.*, Keibel and Mall, Human Embryology, Philadelphia, 1912, ii, 752: *Kermauner, F.*, Schwalbe, Die Morphologie der Missbildungen des Menschen u. der Tiere, Jena, 1909, iii, 253: *Nagel*, Veit, Handbuch d. Gynäkologie, 1st edition, Wiesbaden, 1897, i, 519: *Aschoff*, Pathologische Anatomie, 3d edition, Jena, 1913, ii, 569: *Keith, A.*, Human Embryology and Morphology, 3d edition, London, 1913: and *Ballantyne*, in Eden and Lockyer, System of Gynæcology, London, 1917, i, 215.

[3] *Stolz, M.*, Gynak. Rundschau, 1908, ii, 213.

culation in the uterine or perivaginal venous plexuses. In the latter case the edema may be excessive, leading to the transudation of fluid through the skin, to the formation of vesicles, to superficial erosion, or even to gangrene.

INFLAMMATION. (Vulvitis.)

The skin, mucous membrane, connective tissue, and glands of the vulva may be the seat of inflammation.

Acute Catarrhal Inflammation of the mucous membrane may be induced by a variety of agents; in infancy it is most frequently due to gonorrheal infection. Bacteriological examination will reveal the presence of gonococci in the pus from the urethra and Skene's glands. The adult vulva is very resistant to the local invasion of the gonococcus, but irritating discharges from above, usually cervical, whether due to gonococcal or other forms of cervicitis or to the breaking down of cervical or corporal carcinoma, etc., may by their chemical action set up a severe vulvar irritation. The mucous membrane may be swollen and red, and covered with a mucopurulent exudate. The labia may be swollen, the glands of Bartholin may be involved, and abscesses of the labia may develop. Superficial ulcers usually accompany an acute vulvitis, especially in childhood.

Chronic Catarrhal Inflammation may lead to superficial or deep ulceration of the mucous membrane, to papillary outgrowths, or to thickening of the labia. Suppurative inflammation of the tissue of the labia may occur with a similar process in neighboring parts.

Chronic Gonorrheal Infections in adults usually manifest themselves by the so-called *maculæ gonorrhoicæ*, deep-red indurated areas around the openings of Skene's and Bartholin's ducts. **Erysipelatous inflammation** of the skin of the vulva is frequent in young children; in adults it is less common. Inflammation of the vulvovaginal glands, usually gonorrheal, may be acute and lead to abscesses, or may be chronic and produce induration or cyst formation of the gland or of its duct.

Gangrene may follow erysipelatous inflammation or may occur after parturition; it may accompany severe exhausting and infectious diseases; or it may follow bruises or other injuries. In some forms, such as those known as *noma* and *hospital gangrene*, the destruction of tissue proceeds with extreme rapidity, and in weak children usually proves fatal.[1]

Membranous Inflammation may occur, with or without diphtheria and a similar lesion of the fauces or elsewhere, and is frequently associated with gangrene.

Tuberculous Inflammation, usually with ulceration, occasionally occurs in the vulva. Sometimes nodular elevations, which later may break down and ulcerate, are seen. The ulcerations are serpiginous, with undermined edges.

Syphilitic Inflammation and ulceration are of frequent occurrence on the vulva, particularly on the mucous surfaces, and may lead to considerable destruction of tissue and cicatricial contractions. The *primary*

[1] For a study of noma, see *Blumer, G.*, and *MacFarlane, A.*, Am. Jour. Med. Sc., 1901, cxxii, 527.

lesion of syphilis, the *hard chancre*, is often located at the vulva. It begins as a hard nodule with indurated base, and eventually breaks down, producing a superficial ulcer. Treponema pallidum can be found in the lesion. Of the secondary manifestations, the most common are *mucous patches*, which are superficial lesions of the skin or mucous membrane. *Flat condylomata* (*condylomata lata*) are a late secondary lesion, while *gummata* are more rare tertiary manifestations. *Soft chancre* is less frequent than the hard form, but often occurs.

Venereal Warts (*pointed condylomata, condylomata acuminata*) are excrescences found at the vulvar or anal margin, and are most commonly due to the irritation produced by gonorrheal pus, but are not infrequently the result of innocent discharges. These growths may assume enormous dimensions, reaching the size of two fists, especially during pregnancy. They are soft, finely fissured, elevated excrescences, with a moist surface

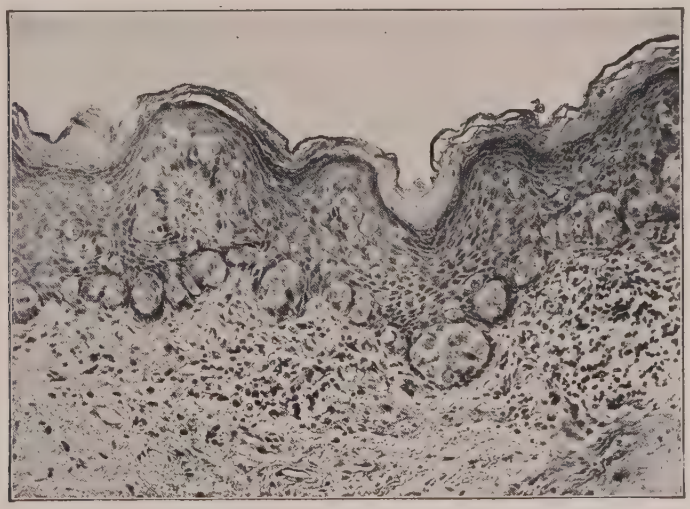


Fig. 602.—Kraurosis Vulvæ.

producing an acrid discharge. Histologically they show a branching connective-tissue framework covered with a thick but otherwise normal layer of epithelium.

Kraurosis is a disease peculiar to the vulva, which is characterized by a progressive atrophy of the adjacent skin and mucosa with secondary shrinkage of the parts.[1] Its etiology is obscure. It usually begins in middle life and in many cases is preceded by intractable pruritus. The labia majora atrophy, the skin losing its pigment, hair, and glands; the labia minora disappear; the urethra is tense, but gaping; and the vulvar orifice may contract so as not to permit the introduction of the tip of a finger. The parts look dry, tense, cracked, and shiny. In many cases, carcinoma (epithelioma) ultimately develops. The subcutaneous con-

[1] *Darger, W.*, Arch. f. Gynec., 1902, lxvi, 637: *Jung. P.*, Ztschr. f. Geburtsh. u. Gynäk., 1904, lii, 13: *Baldy, J. M.*, and *Williams, H. L.*, Am. Jour. Med. Sc., 1899, cxviii, 528.

nective tissue (especially the elastic fibers) atrophies, the papillary projections flatten out, and the Malpighian layer atrophies. In the lower layers of the epidermis, there are often found areas of large clear cells, the significance of which is unknown (Fig. 603).

Closely related to kraurosis, is leukoplakia vulvaris, which is a chronic inflammatory thickening and downgrowth of the vulva resembling leukoplakia elsewhere. The disease is rare and often leads to carcinoma.[1]

Esthiomene is another disease peculiar to the vulva.[2] Its etiology is likewise obscure, although it may eventually prove to be a late manifestation of syphilis. A rodent ulcer develops somewhere along the vulvar circumference, and is always accompanied by much edema and infiltration. Finally, a large number of communicating fistulæ, together with the superficial ulceration, produce great distortion and destruction. The diseased tissue shows no specific characters, resembling that of any indifferent ulcer, though there is often excessive thickening of the vascular walls.

Elephantiasis of the vulva is due to lymphangiectasis and secondary hypertrophy. Rarely, the etiological factor is *filariasis;* more commonly some other interference with the inguinal lymphatic channels (such as extirpation for bubo) may be the cause. Firm, nodular masses of variable size and consistency develop; instances of tumors weighing over twenty pounds have been reported. The surface may be smooth or papillary or even cauliflower-like; secondary ulceration is common. The tissue is edematous, contains dilated lymph-channels, and frequently shows evidences of inflammation (round and plasma cells). The skin is not affected except by secondary changes.

TUMORS.

Fibromata.—Circumscribed fibrous tumors are found in the connective tissue of the labia, mons veneris, perineum, and clitoris, and at the entrance to the vagina.[3] They may attain large size, and, attached only by a pedicle, may hang far down between the legs. The skin is usually movable over the surface of these tumors. They may consist of soft edematous fibrous tissue (*fibroma molle*) or of hard well-marked strands (*fibroma durum*). *Fibromyomata* and *adenomyomata* occur at the insertion of the round ligament.

Papillomata consist of hypertrophied papillæ covered with thick layers of epithelium. They vary in size from that of a pea to that of an apple, and have a cauliflower appearance. **Lipoma, myoma, fibrosarcoma,** and **angioma** are of occasional occurrence in the vulva. A few cases of **melanosarcoma**[4] have been recorded, but later investigations have

[1] *Berkeley, C.*, and *Bonney, V.*, Proc. Roy. Soc. Med., 1909, iii[2], 29: *Bonney, V.*, Lancet, 1908, i, 1465.

[2] For study of esthiomene and secondary elephantiasis vulvæ, see *Stein, A.*, and *Heimann, W. J.* Surg., Gynec., and Obst., 1912, xiv, 345. See also *Kurz, L.*, Jour. Obst. and Gynec. Brit. Emp., 1913, xxiii, 353.

[3] *Leonard*, Bull. Johns Hopkins Hosp., 1917, xxviii, 373 (bibl.).

[4] *Wiener, G.*, Arch. f. Gynäk., 1907, lxxxii, 521; *Meyer, P.*, ibid., 1908, lxxxv, 512, 540; and *Hinselmann, H.*, Ztschr. f. Geburtsh. u. Gynäk., 1908, lxii, 34.

shown that these growths are usually **melanocarcinoma. Chondroma** of the clitoris has been described.

Carcinoma of the vulva may be primary, usually in the form of epithelioma of the clitoris or labia, or may be a metastasis of cancer of the uterus, vagina, etc. The disease usually occurs late in life. The commonest form is the squamous-cell type (epithelioma) with pearl formation. Large, hard tumors which ulcerate early in their course, or flat, superficial rodent ulcers are encountered. The inner side of the labia majora and the clitoris or urethral opening are the commonest sites. Very early involvement of the inguinal and deep lymphatic glands is the rule.[1] Contact cancers, *i.e.*, cancers on apposing surfaces, are not infrequent.

Urethral caruncle, an innocent growth at the mouth of the urethra, should not be confused with carcinoma. Its bright red color (unless changed by trauma or strangulation) and tenderness to touch distinguish it from cancer. Histologically, caruncles are either angiomatous in nature or resemble granulation tissue. They are covered by the transitional urethral epithelium.

Adenoma and **carcinoma** of Bartholin's glands is noted,[2] also the rare **adenoma hydradenoides,**[3] a small growth developing from the sweat-glands and composed of acini containing epithelium in double layers.

Metastatic hypernephroma and **chorionepithelioma** of the vulva have been reported.[4] Histologically these growths resemble the primary tumor. The latter variety is especially prone to hemorrhage and breaking down of the tissue.

CYSTS.

Cysts are found in the connective tissue of the labia majora and minora. They range from the size of a pea to that of a child's head. They may contain serum, colloid material, or purulent or blood fluid, or may have the characters of epidermoid or atheromatous cysts, depending on their origin, which is in many cases obscure. In some cases they are doubtless due to dilatation of lymph-vessels. Cysts may be formed by a stoppage and filling with fluid of the canal of Nuck, or by a dilatation of the ducts or acini of the vulvovaginal glands.[5]

The Vagina.

Malformations.

The vagina may be entirely absent, and the internal organs of generation also absent or imperfectly developed. Either the upper or the lower portion of the canal may be absent, while the remaining portion is present.

The vagina may be closed by an imperforate hymen or by transverse septa at any part of its canal. The canal may be abnormally small without being occluded.

[1] *Küstner, O.*, Arch. f. Gynäk., 1881, xviii, 253; *Teller, R.*, Ztschr. f. Geburtsh. u. Gynäk., 1907, lxi, 309.

[2] *Pape*, Deutsch. med. Wchnschr., 1907, xxxiii, 1620; *Graham*, Edinburgh Med. Jour., 1908, N. S. xxiii, 149; *Spencer, H.*, Proc. Royal Soc. Med., 1913–14, vii[2], 102.

[3] *Ruge, H.*, Ztschr. f. Geburtsh. u. Gynäk., 1905, lvi, 307; *Schröder, R.*, Centralbl. f. allg. Path., 1911, xxii, 529; *Picк, L.*, Virchows Arch., 1904, clxxv, 312.

[4] *Gräfenberg, E.*, Virchows Arch., 1908, cxciv, 17 (bibl.); *Vassmer*, Festschrift f. Orth., Berlin, 1903, p. 237.

[5] For a study of cysts of Bartholin's glands, see *Cullen, T. S.*, Jour. Am. Med. Assn., 1905, xliv, 204.

The vagina may be double, in connection with a double uterus; or, while the uterus is normal, the vagina may be incompletely divided by a longitudinal septum.

Changes in Size and Position

Dilatation of the vagina is produced by tumors, by injury to its supporting structures (birth trauma), and by the accumulation of blood and mucus behind constrictions or obliterations of the canal.

Lengthening of the vagina is produced by any cause which draws the uterus upward. Narrowing may occur as a senile change, may be produced by the pressure of tumors, or may follow ulceration of the wall of the canal through cicatricial contraction (caustics, trauma of labor, infection).

Prolapse of the vagina occurs independently, usually from injury during childbirth, or in connection with prolapse of the uterus. A larger or smaller portion of the canal is inverted and projects through the vulva. The entire circumference of the canal may be inverted and prolapsed, or only the anterior or posterior wall. The prolapse, at first small, may afterward gradually increase in size. In other cases, prolapse of the uterus is primary, and the vagina is inverted by the descent of that organ; or the body of the uterus retains its normal position, while an hypertrophy and lengthening of the cervix alone drags down the vagina.

Cystocele is due to injury of the supports of the bladder, especially of the pubocervical fascial layers. The anterior vaginal wall increasingly protrudes until the entire bladder base, between fixed trigone and cervix, bulges through the vulva, covered merely by the vaginal mucosa.

Rectocele is a similar bulging of the rectum through the torn rectal fascia, the rectum, covered by posterior vaginal wall, protruding first into the vagina, and later pushing its way into the vulva over the perineal body, if this barrier is still intact.

The everted vaginal walls in prolapse, cystocele, and rectocele, show distinct changes due to trauma, the drying effect of exposure to the air, and vascular stasis. Superficial erosions, ulceration, keratinization of the epithelium (epidermization), and edema of the subepithelial tissues develop.

Hernia Intestinovaginalis is commonly a congenital defect, though the lesion may not manifest itself until adult life. The primary condition is a deep position of the bottom of Douglas's cul-de-sac. The peritoneal reflection may extend down to or into the perineal body; when filled with intestine a mass similar in appearance to a rectocele may bulge into the vagina through its posterior wall. The condition is often complicated by *prolapse of the rectum.*

WOUNDS—PERFORATIONS.

Wounds of the vagina are made by penetrating bodies, by forceps and other obstetrical instruments, by the fetus during delivery, or by coitus. Such wounds may heal; or they may give rise to large hemorrhages, or may suppurate and lead to abscesses in the surrounding tissue or leave fistulous openings into the vagina; or they may, by cicatricial contraction in healing, lead to constriction or obliteration of the vaginal canal; or, finally, they may communicate with the peritoneal cavity, producing peritonitis.

Vesicovaginal Fistulæ are usually produced by injuries from instruments or from the fetus during delivery, less frequently by operative injuries arising during hysterectomy, by ulceration of the vagina, bladder, or adjacent connective tissue, or by abscess in the surrounding parts. The sloughing of neoplasms involving the walls of the vagina and bladder may also give rise to fistulæ, especially if the tumors have been

too vigorously treated with radium. The fistulæ form an opening between either the bladder or the urethra and the vagina, allowing the urine to pass into the vagina. Spontaneous cure takes place in a small number of instances. In some cases, the fistula leads into the cervical canal, which allows the urine to empty into the vagina by way of the external os.

Rectovaginal Fistulæ are formed in the same way as the last mentioned, and allow the passage of gas or feces into the vagina. They, also, sometimes heal spontaneously.

INFLAMMATION. (Vaginitis.)

The vaginal canal is the habitat of many bacteria. Saprophytic streptococci and staphylococci, which under favorable conditions, as after injuries, during the puerperium, etc., may develop virulence, are regularly present. Doederlein's acid-forming bacillus is always present and accounts for the acid reaction of the vaginal secretion. From the anus near by, the colon and related groups of bacilli readily gain entrance. It is only because of the impervious character of the squamous epithelium that vaginitis is a rare disease.[1]

Catarrhal Inflammation of the vaginal mucous membrane may be acute or chronic. It is most frequently induced by the gonococcus, but may be due to local irritation or may accompany acute infectious processes. It not infrequently occurs in the new-born. The adult vagina, like the adult vulva, is resistant to the gonococcus; and although a few cases of chronic gonorrheal vaginitis have been reported in adults, they are the exception. In the acute form of inflammation the mucous membrane is swollen and frequently covered with a mucopurulent or a purulent exudation. In the chronic form it may be swollen and covered with a purulent exudation; there may be an exfoliation of epithelium, shallow or deep erosions, or ulcers. Usually the vagina is irritated by discharges flowing down from the cervix or uterine cavity.

Sometimes large shreds or membranes are cast off from the vagina, consisting wholly of exfoliated, flat epithelium.[2] This may be seen after the use of very strong irrigations of mercuric chloride. In other cases, the mucous membrane is thickened, dense, and sometimes pigmented, or it may be roughened, covered with papillæ, or relaxed and prolapsed.

Membranous Inflammation of the vagina may occur after parturition, and in dysentery, typhus and typhoid fevers, diphtheria, scarlatina, measles, and other infectious diseases. The mucous membrane is swollen and covered with a grayish layer of fibrin and pus; and the mucosa and submucosa may be infiltrated with fibrin and pus. The infiltrated portions of the mucosa and submucosa may die and become gangrenous, and thus deep and extensive ulcers may be formed.

Suppurative Inflammation of the fibromuscular coat of the vagina may occur after injuries or in pregnant or puerperal women. Abscesses which

[1] For a study of the flora of the vagina, see *Shaw, E. H.*, Eden and Lockyer, System of Gynaecology, London, 1917, i, 97 (bibl.).

[2] See *McFarland, J.*, Proc. Path. Soc., Philadelphia, 1899, ii, 115.

penetrate into the labia or into the pelvic connective tissue may be formed. In other cases the intense phlegmonous inflammation may lead to the death and casting-off of portions or even of the entire vaginal wall.

Granular Vaginitis manifests itself by numerous, slightly elevated, red, and easily bleeding spots in the vagina. Small nodules composed of round or plasma cells lie beneath the epithelium which is thinned out or deficient over these prominences.

Senile Vaginitis is a concomitant of senile involution. The surface epithelium becomes attenuated and in spots deficient; and consequent agglutination of apposing surfaces occurs, with resultant bands and scars.

Emphysematous Vaginitis.—Anaerobic bacilli developing in the vaginal wall may give rise to small cysts or blebs.

Gangrene of the vagina may occur as a result of membranous or intense suppurative or syphilitic inflammation or from unknown causes. In the form of *noma* it may be very extensive and rapidly destructive. Bichloride of mercury poisoning, resulting either from the ingestion of large doses or from absorption, after vaginal douching with strong solutions, may produce gangrene and ulceration of the vagina, quite similar to mercurial stomatitis.

Tuberculous and **Syphilitic Inflammation,** usually leading to more or less extensive ulceration, may occur in any part of the vagina. Tuberculous inflammation is usually secondary to tuberculosis of other parts, particularly of the vulva, uterus, or rectum. The usual form is an ulcer with undermined edges and miliary tubercles in its margins. Syphilitic ulcers may heal, sometimes leaving marked cicatrices and sometimes not.

TUMORS.

Fibroma,[1] **fibromyoma**[2] and **adenomyoma**[3] are of occasional occurrence in the vagina. **Sarcoma** of the vagina may be pedunculated, nodular, or diffusely infiltrating. All varieties of sarcomata are observed, including the melanotic form,[4] though the spindle- and round-cell type are most common. Early necrosis and ulceration are the rule. **Sarcoma botryoides,**[5] or **grapelike sarcoma,** occurs most often in early childhood, but is occasionally seen in old persons.[6] Soft, grapelike bodies of reddish to grayish color, arising from the cervix, fornix, and vaginal wall, project from the vagina. Penetration of adjacent structures occurs and recurrence after removal is the rule. On section, the growths are found to be composed of myxomatous tissue with smooth or even striated muscle cells, covered by normal vaginal surface epithelium. These growths are **mixed tumors,** often **rhabdomyosarcomata** (Fig. 603). A **teratoma** has

[1] *Lewers, H. N.*, Am. Jour. Obst., 1895, xxxi, 277.
[2] *Ries, E.*, Am. Jour. Obst., 1902, xlv, 265; *Smith, R. B.*, ibid., p. 145.
[3] *Kleinhaus, F.*, Ztschr. f. Geburtsh. u. Gynäk., 1904, lii, 266.
[4] *Boldt, H. J.*, Am. Jour. Obst., 1906, liv, 550.
[5] *Pick, L.*, Arch. f. Gynäk., 1894, xlvi, 191; *Wilms*, Die Mischgeschwülste, Leipzig, 1900; *Thomas, T. G.*, Am. Jour. Obst., 1874–75, vii, 51; *Schuchardt, K.*, Virchows Arch., 1889, cxvii, 262; *Kolisko, A.*, Wien. klin. Wchnschr., 1889, ii, 119; *Möncxeberg, J. G.*, Virchows Arch., 1907, clxxxvii, 47; *Amann, J. A.*, Arch. f. Gynäk., 1907, lxxxii, 746; *Meyer, R.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1905, ix[2], 518.
[6] *Puech* and *Massabuau*, Ann. de gynec. et d'obst., 1908, 2d ser., v, 306.

been described and a few cases of **endothelioma,**[1] the latter being, in all probability, carcinomata of unusual morphology. The only demonstrable metastases from a **hypernephroma** may appear in the vagina.[2]

Papillomata are of infrequent occurrence, resulting from chronic inflammation. They are usually of gonorrheal origin and most frequent in pregnancy. Histologically, they are identical with papilloma of the vulva.

Carcinoma of the vagina is usually secondary to cancer of the cervix. The rare primary carcinomata[3] usually develop on the posterior surface

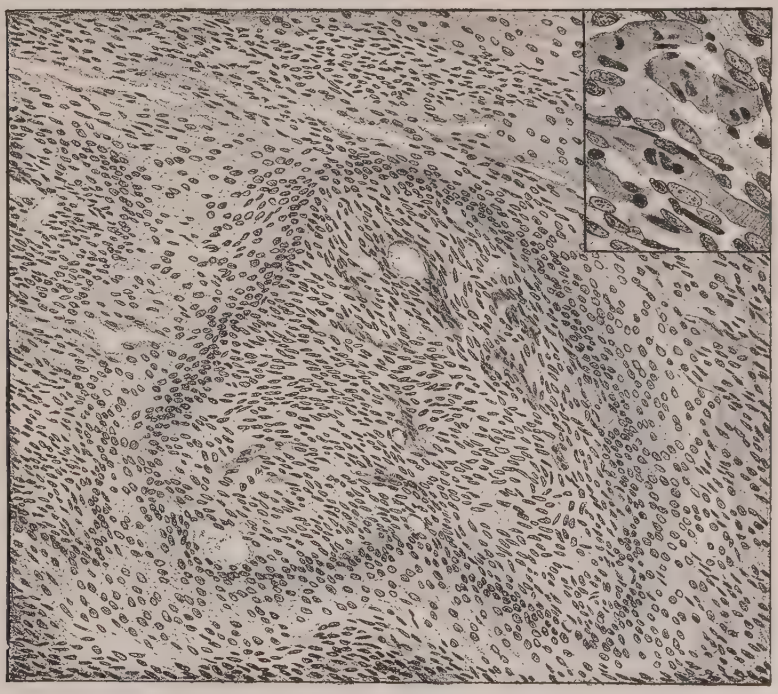


FIG. 603.—SARCOMA BOTRYOIDES.
Small insert in corner of cut shows more highly magnified striated muscle fibers.

of the upper third of the vagina in women past the menopause. The tumors may be slightly elevated and papillary, or cauliflower-like, or, most rarely, diffusely infiltrating. Early involvement of the paravaginal tissues, the parametria, and the cervix occurs. The most frequent form is medullary or squamous-cell carcinoma, though adenocarcinoma arising from Gartner's duct or other gland remnants has been reported.

LEUKOPLAKIA occurs just as in the oral cavity. White, "asbestos-like" plaques, with glistening surfaces, are noted. The condition is regarded as a "precancerous"

[1] *Raschkes, H.*, Centralbl. f. allg. Path., 1903, xiv, 657; and *Jellett, H.*, Jour. Obst. and Gynec. Brit. Emp., 1907, xii, 285.

[2] *Gellhorn, G.*, Amer. Jour. Med. Sc., 1918, clvi, 94.

[3] *Broun, L.*, Am. Jour. Obst., 1902, xlv, 706; *Taylor, H. C.*, ibid., 1906, liv, 860; *Menge*, München. med. Wchnschr., 1906, liii, 30.

manifestation. Great increase in the superficial layers of the epithelium produces the appearance as in the vulva.

CYSTS.

These are not very common and may be small or as large as a hen's egg. They may be lined with flattened epithelium and contain serous or viscid, dark-colored or transparent fluid.[1] Most vaginal cysts occur in the anterior wall, resulting from remnants of Gartner's ducts. They may extend upward in the subperitoneal tissues alongside the cervix. They usually have thin walls, and project as bluish prominences into the vagina. They are lined with epithelium of very varied character.[2]

PARASITES.

Among the animal parasites **Oxyuris** and **Trichomonas vaginalis** are of occasional occurrence. Among the vegetable forms **Oidium albicans,** particularly in diabetes, and **Leptothrix** are occasionally seen, while various forms of **bacteria** are regular inhabitants, especially Doederlein's bacillus. Staphylococcus and Streptococcus pyogenes have been found many times in the normal vagina, and while these and other bacteria may be harmless in the normal vagina, should conditions favoring their growth or an increase in their virulence occur, as, for example, after delivery, serious infectious processes might follow.[3] The rôle of the gonococcus as an excitant of catarrhal inflammation is well established.

The Uterus.

Malformations.

The uterus, tubes, and vagina may be entirely absent, with or without absence of the external genitals; or the uterus, alone or with the upper part of the vagina, may be absent.

The uterus may be only rudimentary while the vagina is normal; it then appears as a flattened solid body with solid cornua. Or there may be two cornua joined at their lower extremities so as to form a small double uterus (Fig. 604); the uterus may be represented by a small sac, which may or may not communicate with the vagina; or there may be a very small uterus, with thin muscular walls and two large cornua.

Only one of the cornua which should form the uterus may be developed, while the other is arrested in its growth. The uterus is then a long, cylindrical body, terminating above in one tube. On the side where the horn should have been developed there is no tube, or only a rudiment. Both ovaries are usually present.

The two cornua may be fully developed, but their lower ends may remain separated and form a double uterus. An entire separation into two distinct uteri and vaginæ is rare. More frequently the uterus consists of one body, divided by a septum into two cavities. There are then two cervical portions of the uterus projecting into a single vagina, or each into a separate vagina; or there is only a single cervix. The septum in the uterus may be complete or only partial.

[1] *Stokes, J. E.*, Johns Hopkins Hosp. Rep., 1899, vii, 109 (bibl.); and *Cullen, T. S.*, Bull. Johns Hopkins Hosp., 1905, xvi, 207.

[2] *Pierce, F. E.*, Am. Jour. Obst., 1904, l, 507, 534; *Pollak, E.*, Ztschr. f. Geburtsh. u. Gynäk., 1904, lii, 428.

[3] See *Shaw, E. H.*, Eden and Lockyer, System of Gynaecology, London, 1917, i, 97 (bibl.).

The uterus may be abnormal in size or be variously flexed; the cervix may be solid or may be closed by the vaginal mucous membrane; or the cervix may have an abnormal form with a small opening or canal.

Changes in Size.

In the new-born infant the uterus is small, the body flattened, the cervix disproportionately large and the cervical canal dilated with mucus. During childhood the organ increases in size, but the body remains small in proportion to the cervix. At puberty the shape changes and the body becomes larger.

At every menstruation the uterus is somewhat swollen and congested. After pregnancy it does not return to its virgin size, but remains somewhat larger. In old

Fig. 604.—Uterus Bicornis.

age it gradually becomes smaller; its walls are harder and more fibrous; and the cervix atrophies.

Abnormal Smallness of the uterus is sometimes found as an arrest of development. It may result, however, from lactation atrophy, from old age, or from chronic exhausting diseases. Its cavity may be smaller than normal, or distended with mucus. Large myomata sometimes induce atrophy of the uterine wall. Atrophy of the vaginal portion of the uterus is sometimes observed after repeated pregnancies. Narrowing and obliteration of the cavity of the uterus and of the cervix are usually produced by chronic inflammation.

Enlargement of the Uterus may be due to premature sexual development. It is accompanied by abnormally early development of all the sexual organs and func-

tions. The uterus may be enlarged in connection with heart disease, prolapse, and abnormal flexions, chronic inflammations, repeated pregnancies, myomata, and accumulations of blood or mucus in the uterine cavity. Enlargement of the vaginal portion alone may occur. One or both lips of the cervix may be uniformly increased in size, or they may be lobulated.

Dilatation of the uterus is produced by accumulations of blood, mucus, or pus in consequence of narrowing or obliteration of the cervix or vagina. The uterine walls may retain their normal thickness, or be thickened or thinned. The most frequent site of the stneosis is the os internum. The retained contents after a time change in character, forming a thin, serous fluid—*hydrometra;* or they may be mixed with blood. The dilated uterus may be of enormous size. If both os internum and os externum are closed, the cervical cavity also may be dilated and the uterus have an hour-glass shape (Fig. 605); or the dilatation may be limited to the cervix. If the obstruction is

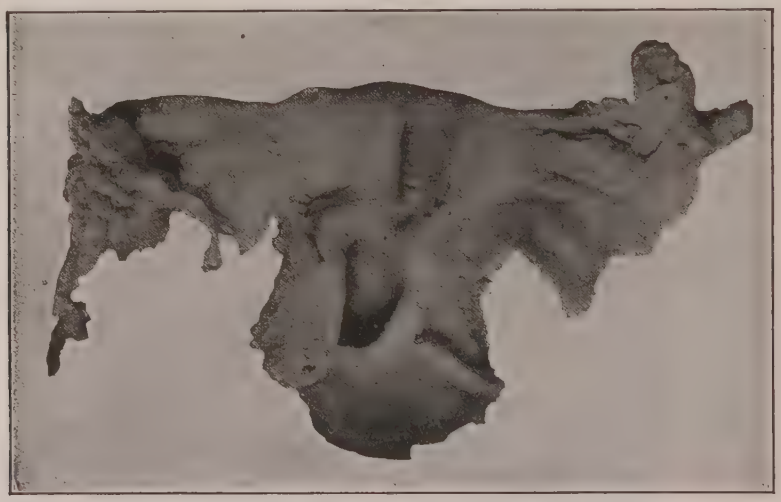


FIG. 605.—HOUR-GLASS UTERUS.
Showing a small uterus with distention of the cavities of the body and cervix from fibrous-tissue contraction at the os externum and the os internum.

not complete, the retained fluid may escape into the vagina and be followed by a fresh accumulation. If the obstruction be in the vagina, the uterus and vagina may form a large, flask-shaped body, and the line of demarcation between cervix and vagina be lost.

Accumulation of menstrual blood in the cavity of the uterus—*hematometra*—is usually due to imperforate hymen, in which case hematocolpos precedes the hematometra. Rarely, it may be due to congenital stenosis of the cervix or vagina, and then may be very great. If the fluid is not evacuated by surgical interference there may be either rupture or ulcerative perforation of the uterus. The blood may escape into the abdominal cavity, or be shut in by adhesions, or perforate into the bladder or intestines. Sometimes the blood passes into the Fallopian tubes, dilates them, and escapes through their abdominal ends.

Changes in Position.

The body of the uterus may become fixed in an abnormal position, while the situation of the cervix is unchanged.

FLEXION.—The body may be bent forward—*anteflexion*, generally regarded as the normal position; backward—*retroflexion* (Fig. 606); or sideways—*lateral flexion*. The

flexion may be slight, or so great that the neck and body form an acute angle. Anteflexion is the most common variety, and that in which the flexion is greatest. Peritoneal adhesions, flaccidity of the uterine walls, particularly after delivery, atrophy of the walls, ovarian and other tumors, etc., are the usual causes of abnormal flexion.

VERSION of the uterus consists in an abnormal inclination of the long axis of the organ to that of the vagina. The uterus may be inclined backward, forward, or to one side.

Retroversion is the most common displacement. The fundus uteri is directed backward and downward, the cervix forward and upward. This condition is found

FIG. 606.—RETROFLEXION OF UTERUS.
Small cysts may be seen in the mucous membrane of the body.

in various degrees; in the highest the fundus lies in Douglas's cul-de-sac with the cervix upward, so that the axis of the uterus is parallel to that of the vagina, but in a direction nearly opposite to the normal. Abnormal looseness of the uterine ligaments, abnormally large capacity of the pelvis, enlargement or tumors of the uterus, and early pregnancy, are some of the more common conditions under which this lesion occurs.

Anteversion, an inclination of the fundus forward and downward, and of the cervix backward and upward, is not common and seldom reaches a high degree.

Lateroversion is not very common as a simple lesion, but is not infrequently combined with other displacements. It may be produced by congenital or inflammatory shortening of one of the broad ligaments, by adhesions, or by the pressure of tumors.

Uncomplicated versions produce few symptoms. The lesion producing the version, as adhesions or impactions of a growing pregnant uterus, may cause serious or

fatal disturbances; exfoliative cystitis, perforation of bladder, dilatation of the ureters, hydronephrosis, and fatal obstruction of the bowels may follow. If pregnancy exist, abortion may take place, or the inverted uterus may be forced through the peritoneum and posterior wall of the vagina and project through the vulva. In the non-pregnant uterus, pressure on the veins results, and chronic stasis of the organ may follow.

Prolapsus uteri consists of a descent of the uterus into the vagina. The uterus may be only slightly lowered or it may project at or beyond the vulva (Fig. 607). In complete prolapse we find a tumor projecting through the vulva, covered by the distended vagina, and presenting the opening of the os externum near its center. The bladder and rectum may be drawn down with the vagina, or may remain in place. The exposed cervix and vagina usually become inflamed and sometimes ulcerated, or the mucous membrane may become thickened. The lesion is frequently complicated by hypertrophy of the cervix.

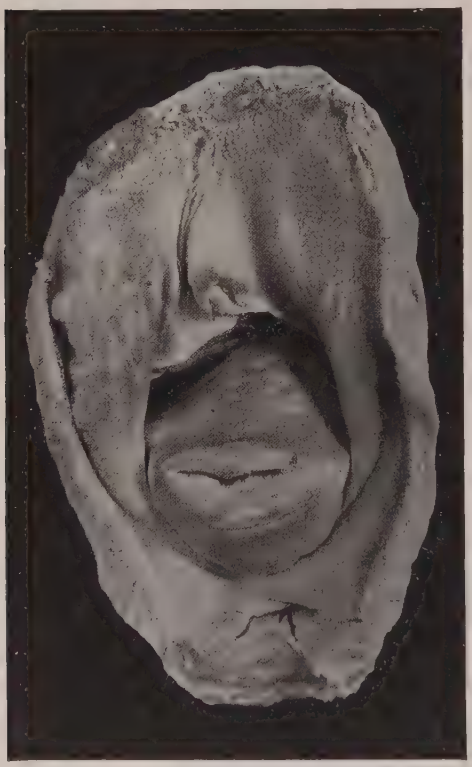


Fig. 607.—Prolapse of Uterus.
The cervix projects from the vulva and there are small ulcerations about the os externum.

Gradual prolapse, which is most frequent, may be due to an increased weight of the uterus, as in pregnancy, in the presence of tumors, etc., or, most generally, to injury of the uterine supports, especially tearing and stretching of the pericervical connective tissue during labor. Sudden prolapse is most apt to occur following a severe and sudden lifting effort by a person whose uterine supports have been weakened by parturition or long wasting illness. In nulliparæ prolapse is a great rarity; it is occasionally noted, however, in subjects afflicted with spina bifida, of either the occult or the overt variety.

Elevation of the uterus is produced by mechanical causes crowding or dragging it upward, as adhesions, tumors, etc. The vagina is drawn up and lengthened, and the vaginal portion of the cervix may be obliterated. The commonest causes are large fibroid tumors and ovarian cysts with short thick pedicles.[1]

Inversion of the uterus consists of an invagination of the fundus. The fundus may be invaginated into the body, the fundus and body into the cervix, or the entire organ into the vagina. It usually occurs when the uterine walls are relaxed, and may be due to traction on the placenta during parturition. It may take place spontaneously after parturition. Acute intrapartum cases are often fatal from shock, hemorrhage, or sepsis. In rare instances, the onset is survived, and the condition becomes chronic. Inversion may be produced by intrauterine tumors, such as a pedunculated fibroid arising from the fundus The mucous membrane of the inverted organ is frequently inflamed, particularly when the inversion is complete. The epithelium may become squamous and lamellated in type.

[1] For details concerning the various types of displacements, see *Eden* and *Lockyer*, System of Gynaecology, London, 1917, ii, 595, 627, 687.

HERNIÆ of the uterus are rare. *Ventral herniæ* may occur during the latter months of pregnancy, the peritoneum, aponeurosis, and skin being forced outward to form a sac in which the uterus lies. *Crural herniæ* are produced by the drawing down of the uterus and ovaries into the sac of a femoral hernia. *Inguinal herniæ* may be produced in the same way or may be congenital. *Ischiatic herniæ* have been seen. Pregnancy may occur in the uterus while it is within a crural or inguinal hernia.

RUPTURE AND PERFORATION.

Rupture of the unimpregnated uterus is rare. It may occur, however, when the uterine cavity is distended with blood or serum, or in connection with large myomata of the uterine walls. It occurs during operative dilatation of the cervix.

In the gravid uterus ruptures have been seen in nearly every month of pregnancy, but most frequently toward the end. The rupture may be due to a thinning of the uterine wall by tumors, by deep penetration of placental villi, or by violent contusions, or as the result of cicatricial contraction of the os. It most frequently takes place during parturition. Malpositions of the fetus, narrowing of the pelvis, protracted labor, thinning of the uterine wall from tumors, forcible use of the forceps and other instruments, and attempts at version are the ordinary causes. The rupture may be in the body of the uterus or in the cervix or in both; it may be large or small; it may extend completely or only partly through the uterine wall; it may extend into the peritoneal cavity or be extraperitoneal. The consequences of partial rupture are hemorrhage, gangrenous inflammation of the edges of the rupture, peritonitis, and, usually, death. In some cases, the rupture cicatrizes, and the patient recovers. Complete rupture usually leads to death in a short time. The fetus may escape partly or completely into the abdominal cavity. If the patient survive the immediate shock, fatal peritonitis usually soon ensues. In rare cases the fetus is shut in by adhesions, and the patient survives.

Perforations of the uterus may be produced by carcinoma, by abscesses in its neighborhood, by ovarian cysts, and by instrumentation.

HYPEREMIA—UTERINE HEMORRHAGE.

Hyperemia.—Aside from the active menstrual hyperemia, the uterus may be hyperemic in acute and chronic inflammation, as a result of displacement of the organ, and in certain forms of heart disease. The organ is usually enlarged, the mucous membrane is swollen, and the veins are more or less evidently dilated. Edema may be associated with hyperemia.

Hemorrhage.—Effusion of blood into the cavity of the uterus occurs normally at the menstrual periods. For the abnormalities to which this function is subject we refer to works on gynecology. Effusions of blood at other than the menstrual periods may be associated with numerous causes: *local intrauterine* (such as tumors, polypi, fibroids, and pregnancy); *local neighboring* (pressure from intraligamentous cyst, cyst with twisted pedicle, ectopic gestation); *acute systemic* (infectious diseases, as

typhoid fever, typhus fever, and scurvy); and *chronic systemic,* with resulting general circulatory disturbances, as decompensated heart lesions. A large number of hemorrhages are due to functional ovarian disturbances.

ATROPHY, DEGENERATION, ETC.

Atrophy of the uterus occurs as a physiological process in old age. The glands of the endometrium are few, the interstitial tissue is relatively

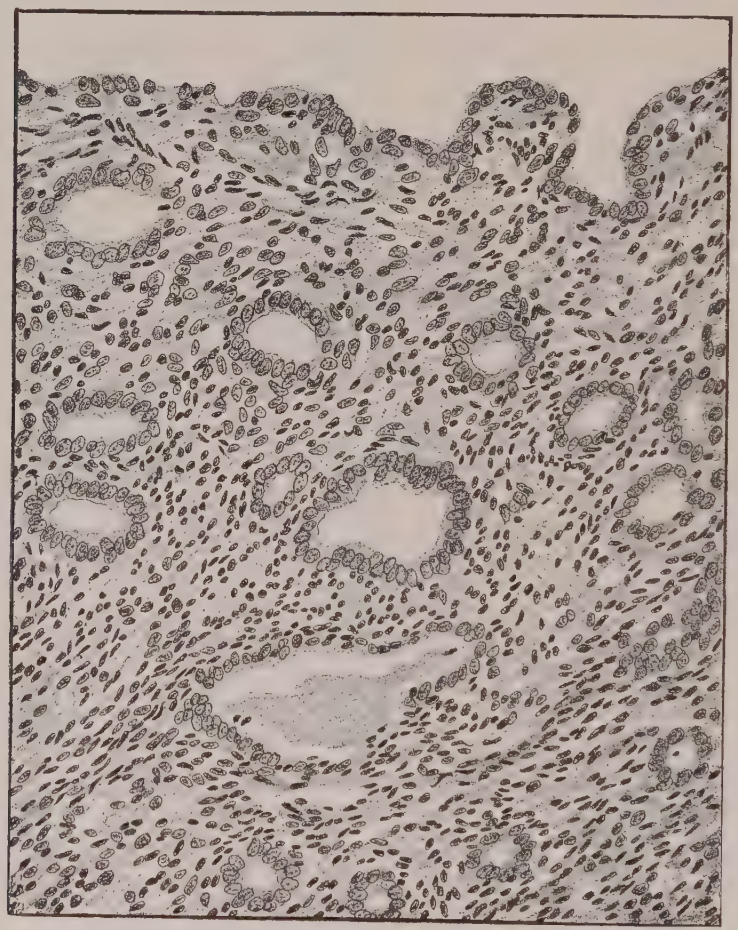


Fig. 608.—Senile Atrophy of Endometrium.

increased (Fig. 608). It may be associated with severe general or infectious diseases or may follow removal of the ovaries. It may follow pregnancy apparently as an excessive involution process (lactation atrophy). Advanced degrees of atrophy are noted in the later stages of many diseases of the glands of internal secretion, especially in hypopituitarism.[1]

[1] *Goetsch, E.*, Surg., Gynec., and Obstet., 1917, xxv, 229.

Fatty Degeneration may occur in connection with inflammatory changes, in acute infectious diseases, and in phosphorus poisoning.

Amyloid Degeneration in the uterus is of rare occurrence. It may affect the muscle fibers or the walls of the blood-vessels.

Hyaline Degeneration of the walls of the blood-vessels and the connective tissue is occasionally seen, but is much more frequent in myomatous uteri.

INFLAMMATION. (Metritis and Endometritis.)

I. Inflammation of the Unimpregnated Uterus.

A. Of the Corpus Uteri.

Acute Catarrhal Endometritis.—In this disease, which in its lighter grades may leave but little alteration after death, the mucous membrane

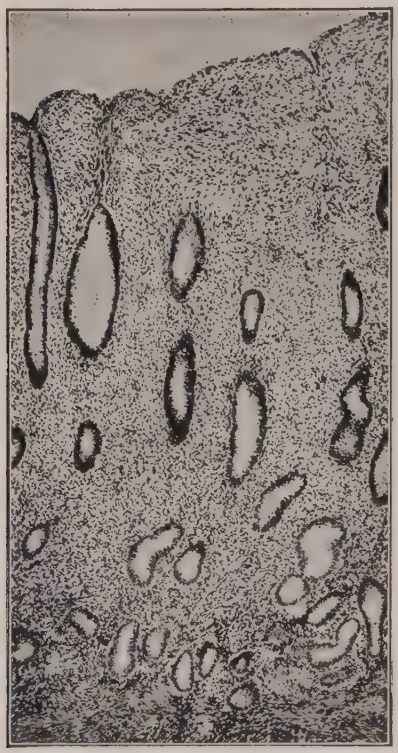


Fig. 609.—Interval Phase of Endometrium.

is swollen and hyperemic, and is sometimes the seat of punctate hemorrhages. The epithelium may be degenerated and may desquamate, and the mucosa may contain an undue quantity of polynuclear leucocytes. The surface is more or less thickly covered with mucopurulent exudate. In severe cases shreds of mucous membrane may be exfoliated. The

lesion is usually most marked in the mucous membrane of the body, but it may involve the cervix at the same time, or the cervix alone. The body of the uterus may be soft, swollen, and hyperemic. The condition is most frequently of gonorrheal origin, though the introduction of unclean instruments may also be the cause. On the whole, the non-pregnant uterus rapidly rids itself of most bacteria except the gonococcus.

In *membranous dysmenorrhea* there may be an expulsion, with more or less blood, of membranous masses consisting of fibrin mingled with blood and leucocytes, or of exfoliated superficial layers of endometrium. The exfoliated epithelium is frequently much flattened so as to resemble the vaginal epithelium.[1] The decidual reaction in interstitial tissue is occasionally very considerable, so that pregnancy may be suspected; but the cells never reach the size of those seen in pregnancy. Membranous dysmenorrhea appears to be a purely functional condition, possibly due

FIG. 610.—PREMENSTRUAL ENDOMETRIUM.

to an excess production of the menstrual decidual reaction. It is a common sequel of infantile habitus.

Chronic Endometritis.—What was formerly classed as chronic endometritis, is to-day recognized to be due mainly to various functional and normal cyclical changes of the mucosa. The symptoms usually assigned to endometritis—hemorrhage and leucorrhea—are due to other causes. Hemorrhage results from ovarian stimuli; leucorrhea from cervical inflammation. The ovarian overfunction, in rare instances, is due to ovarian or tubo-ovarian inflammations, but most commonly it is a disturbance of internal secretion (primarily or secondarily of ovarian origin).

Normal Cyclical Uterine Changes.—Subject to ovarian influences, the uterus, after the onset of puberty, undergoes a "monthly" cycle. (Actually, the cycle varies from twenty-one to thirty-five days, the average being twenty-eight days.) According to the histological changes,

[1] See *DeWitt, L. M.*, Am. Jour. Obst., 1900, xlii, 308 (bibl.); *Ascheim, S.*, Arch. f. Gynäk., 1906, lxxx, 320.

the phenomena are best divided into three stages, though some writers describe a fourth stage (*postmenstruum*).

1. The *Interval* is the period following menstruation, during which the mucosa is thin and pale, its glands are circular and far apart, and their epithelium is low columnar, inactive, and regular. The stroma is dense; the cell bodies are not distinguishable; and the nuclei are closely packed (Fig. 609). This picture corresponds to the "normal endometrium" of older authors, and also to "chronic interstitial endometritis."

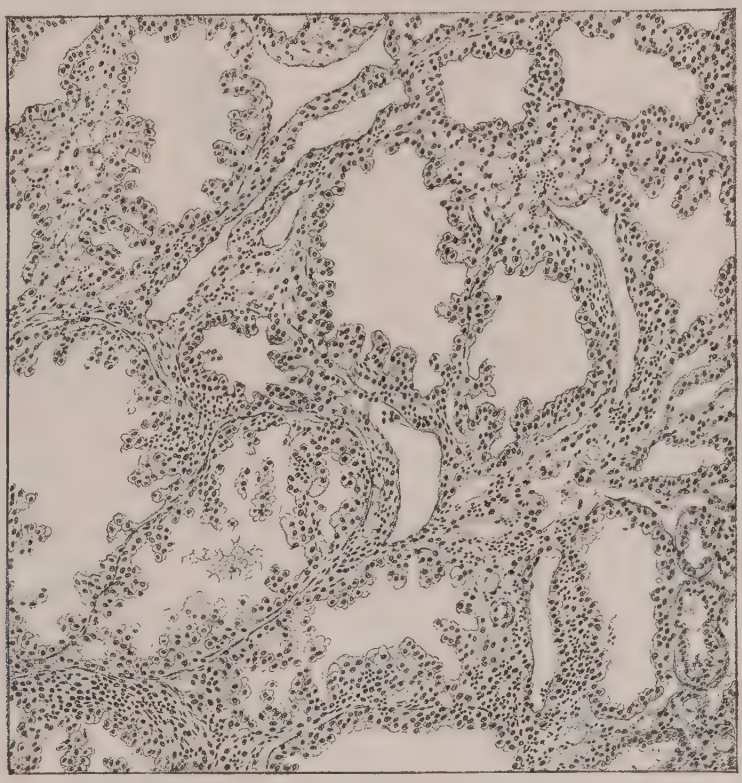


Fig. 611.—Premenstrual Phase of Endometrium.

2. The *Premenstruum* is characterized by thickening of the mucosa (Fig. 610). The mucous membrane, on section, shows three distinct layers, a superficial layer, in which the stroma is edematous and decidual in character, a spongy layer, in which the tortuous corkscrew glands lie closely packed, in some areas even in actual contact, and a thin basal layer, close to the uterine musculature, harboring the gland fundi, in which very little glandular or stroma change has occurred (Fig. 611 and 612).

The key-note to the premenstruum is *secretory activity*. In the early part of this change, mitoses in the epithelium abound. In consequence of an increased number of cells and the distention of the old and new

cells with secretion, the glands become tortuous and corkscrew in shape; the cells are crowded out into the gland lumina, and their superficial boundary is irregular and feathery, forming so-called "pseudopapillæ," and the gland lumen contains secretion. The capillaries, especially those

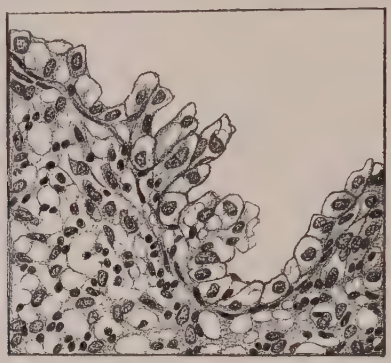


FIG. 612.—PREMENSTRUAL PHASE OF ENDOMETRIUM.
Highly magnified glands.

in the outer layers of the mucosa, distend; and first the circumpapillary, and later the entire stroma becomes decidual in character. This implies that the round cells acquire epithelioid characteristics. Their cell bodies enlarge; the cell boundaries grow distinguishable; and the nucleus stains less deeply. This phase was formerly classified as "glandular endometritis."

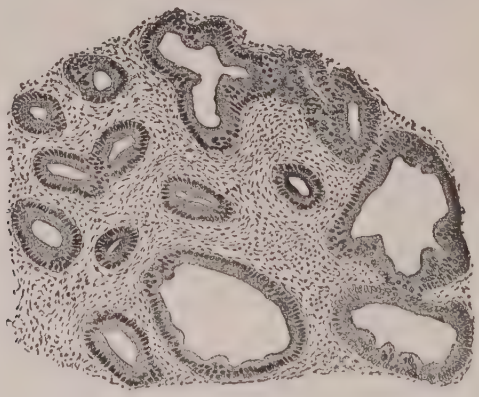


FIG. 613.—GLANDULAR AND CYSTIC HYPERPLASIA OF THE MUCOUS MEMBRANE.
The stroma of the mucosa is increased in amount and is dense and fibrous in texture.

3. *Menstruation* is ushered in by an increase of the capillary engorgement. Red blood-cells permeate between the stroma cells, and finally obscure them. The glands rapidly empty themselves of their secretion, and the glandular epithelium, a few hours after menstruation has begun, reassumes a resting columnar appearance. Blood-cells in increasing numbers accumulate in the uterine cavity, mixed with secretion, and

produce the phenomenon known as menstruation. Occasional small areas of the surface epithelium are raised up by the blood-cells, until the pressure produces a minute epithelial rupture, but large areas of denudation do not occur. *The picture in normal menstruation is identical with that in irregular hemorrhages, because in both instances the bleeding is due to ovarian influences.*

As the onset of the cyclical changes is not abrupt and as different parts of the endometrium do not respond at exactly the same rate, one part of the cavity may show a picture of the late interval, for example; another, one of the beginning or even of the advanced premenstrual change.

Bleeding Due to Ovarian Hyperfunction (*Menorrhagia* or *Metrorrhagia*).—The histological picture during the hemorrhagic period does

Fig. 614.—Polypoid Endometrium.

not differ from that seen in normal menstruation. During the interval and premenstruum, the cyclical changes may be exaggerated; the three distinct layers described above, under the premenstruum, may not be clearly marked; and, especially in the hemorrhages of puberty and the preclimacterium, cystic dilatation of the glands is common. Considerable familiarity with the normal conditions is required to distinguish these slight and, after all, mainly quantitative changes.

Polypoid Endometrium is a condition in which the excessive and continued ovarian hyperfunction has produced a diffuse hyperplasia of the mucosa which throws it into projecting folds; later, polypi may develop, so that finally the uterine cavity may be filled with soft knobby masses (endometritis fungosa of Ohlshausen, Fig. 614). The mucosa is edematous and many dilated glands are seen. Hemorrhage is the usual symptom.

Subacute and Chronic Endometritis are probably of not very frequent occurrence, are of very little clinical significance, and can be recognized only when plasma cells are found.[1] Even when such lesions are present, the usual cyclical changes are unaffected.

Membranous Endometritis (*Endometritis dissecans*).—This form of inflammation is not very common. It occasionally occurs in the puerperal uterus and in acute infectious diseases. It sometimes involves the vulva, vagina, and Fallopian tubes. It may coexist with membranous inflammation of the colon.

Tuberculous Endometritis.—This is not uncommon, and usually occurs as part of tuberculous inflammation of the genitourinary tract, especially of the Fallopian tubes. The disease occurs in two forms, the diffuse caseous and the discrete nodular, although both varieties may be encountered in the same uterus. Tuberculous pyometra may be produced if the cervix becomes obstructed. A part or the whole of the cavity of the uterus may be lined with a rough, yellowish or gray, caseous mass, which may deeply involve the muscular walls of the organ. At the edges of the ulcerating caseous areas there may be typical miliary tubercles, or these may be scattered through the otherwise intact mucosa.[2] The peritoneal surface of the uterus may be studded with tubercles, usually as part of a tuberculous peritonitis (*tuberculous perimetritis*).

Pyometra.—If the cervix becomes stenosed from trauma, cauterization, or tumor formation (chiefly carcinoma), and a severe bacterial invasion develops in the uterus, the corporal cavity is distended by pus. The mucosa first loses its surface epithelium, and later changes into a pyogenic membrane (Fig. 615). Occasionally, the surface epithelium persists and changes into *squamous epithelium.*

Syphilitic Endometritis.—This condition is rare and but few authentic cases are on record. It is characterized by a diffuse thickening of the mucosa and gummatous infiltrations.

Acute Metritis is usually associated with acute catarrhal endometritis. The organ is swollen, succulent, and congested; the mucous membrane is covered with mucopus; and the peritoneal coat is congested. There may be small extravasations of blood in the wall or cavity of the uterus. The inflammation, in rare cases, becomes suppurative, and abscesses are formed in the uterine wall; these may perforate into the peritoneal cavity or into the rectum. Residua of the process leave connective-tissue scars in the musculature.

Perimetritis.—The peritoneal coat of the uterus may be inflamed, with the production of membranous adhesions or of pus. The adhesions may be small or very extensive, and, owing to their contractions, may cause various distortions and displacements of the pelvic organs. The inflammation is usually an accompaniment of chronic salpingitis and is due to

[1] This is the view expressed by *Hitschmann* and *Adler* in their original monograph; in a later paper, however, they modified this opinion (Arch. f. Gynäk., 1913, c, 233). Others think that the presence of plasma cells is not necessary for a diagnosis of endometritis, though they indicate an inflammatory process. See *Fothergill, W. E.*, Brit. Med. Jour., 1911, i, 559; *Schickele, G.*, and *Keller, R.*, Arch. f. Gyn.k., 1911–12, xcv, 586: *Buttner, O.*, ibid., 1910, xcii, 781: and *Albrecht, H.*, and *Logothetopulos, K.*, Frankf. Ztschr., 1911, vii, 150.

[2] *Cullen, T. S.*, Johns Hopkins Hosp. Rep., 1895, iv, 441.

repeated attacks of pelvic peritonitis, arising from the discharge of infective material from a partially closed tube. In prostitutes, such adhesions are of very common occurrence.

Parametritis —The connective tissue about the uterus, between that organ and the reflexions of the peritoneum, may be the seat of suppurative inflammation. This most frequently ends in recovery, usually with the formation about the uterus of dense connective-tissue scars which draw that organ into the hollow of the sacrum or toward one of the pelvic walls.

The subperitoneal tissues surrounding the uterus are of broad extent and may be divided into anterior, posterior, and lateral parametria, although they are directly continuous with each other and with the pre-

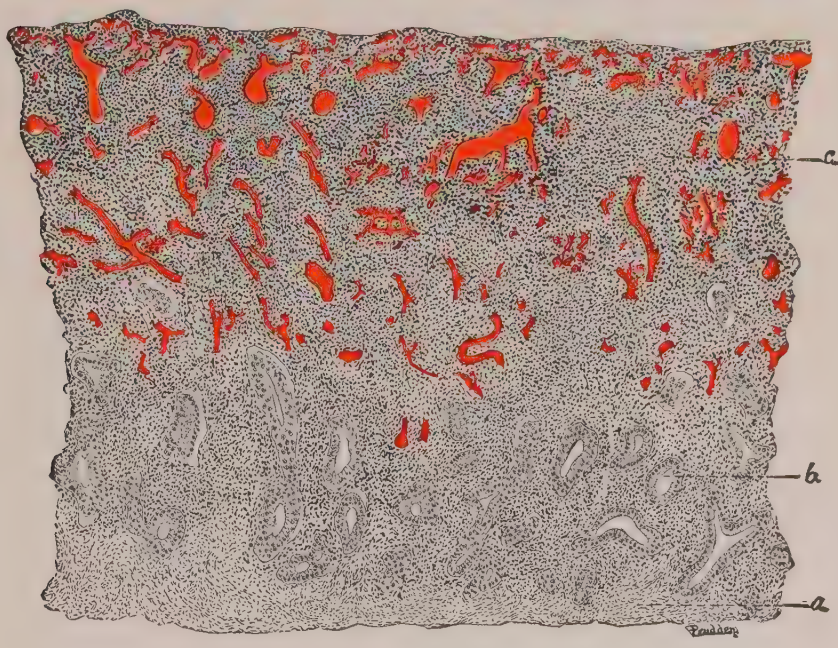


FIG. 615.—PYOMETRA.

a, Uterine muscle tissue; *b*, mucous membrane of uterus; *c*, new-formed vascular tissue.

vesical, retroperitoneal, and iliac connective-tissue strata. These anatomical relations and the course of the lymphatic channels account for the direction of extension taken by phlegmons. Infections far down in the base of the broad ligaments spread into the rectovaginal septum and the posterior parametrium, and along the lateral pelvic wall; those of the upper broad ligament extend upward upon the flare of the ilium and above Poupart's ligament; prevesical infections progress alongside the bladder toward the space of Retzius, etc.

The vast majority of phlegmons are due to the streptococcus. Entrance is afforded to the germ by unclean cervical instrumentation, by birth trauma followed by infection, and by acute endometritis. An acute

lymphangitis and cellulitis is set up, rapid exudation producing more or less voluminous tumor-like masses. Depending upon the virulence of the process, absorption or abscess formation takes place. The affected tissues are doughy, yellowish-white, and succulent.

Pus exudes from the lumen of cut lymphatics; the veins may be filled with dark red or purulent thrombi. If abscesses form, they may perforate into the vagina, cervix, or rectum. The process may produce a general systemic thrombophlebitis (pyemia). In milder cases, abscesses do not form, and resolution with resultant scar formation (strands in the base of the broad ligament) occurs.

Chronic Metritis may follow acute metritis or may accompany acute or chronic endometritis, and is dependent upon similar conditions: subinvolution, displacements, the presence of tumors, active irritants, etc. The uterus is enlarged, the wall congested, thickened, and soft, or, owing to the new formation of connective tissue, hard and dense. The lesion is usually accompanied by chronic perimetritis and parametritis; in fact, a separation of the three conditions is somewhat artificial.

B. Of the Cervix Uteri.

Inflammations of the cervix uteri produce hypersecretion (leucorrhea), erosions of the vaginal portion, and cystic hyperplasia (ovuli Nabothi). Specific inflammations—syphilitic and tuberculous—are also found.

Acute Endocervicitis manifests itself by profuse mucopurulent discharge. The cervical glands are found distended with secretion, the surface epithelium of the vaginal portion is succulent, and the stroma is infiltrated with leucocytes and round cells. Gonorrhea is the most frequent cause.

Chronic Endocervicitis.—In this condition the mucopurulent discharge persists, and glands whose openings have been closed off distend, their high columnar epithelium gradually becoming cuboidal and flattened as the intracystic pressure increases. The stroma is fibrous, with round-cell infiltration.

Erosions are the result of cervical inflammation. Normally, the cylindrical epithelium lining the cervical canal ends at the margin of the external os, where an abrupt transition to stratified squamous epithelium takes place (Fig. 616). Under the influence of the irritating cervical discharge (to which the cylindrical cervical epithelium is most resistant), the squamous covering of the vaginal portion is cast off and the unprotected cervical stroma is exposed. The cervical columnar epithelium rapidly covers the epithelial defect. The resultant bright red, granular, easily bleeding areas around the external os are called *erosions.*

Healing of erosions takes place by resubstitution of squamous epithelium, which may creep under the persistent cylindrical epithelium or may crowd it out. The squamous epithelium often grows over cervical gland openings, or grows downward into wide open gland lumina (Fig. 617). This struggle for supremacy frequently imparts an appearance of great

activity to the epithelium, which may assume bizarre shapes and configurations causing the inexpert to make a diagnosis of carcinoma.

Syphilis of the cervix takes the form of chancre, of maculopapular lesions, and, rarely, of gummata, depending upon the stage of the disease.

Tuberculosis produces undermined ulcers and papillary excrescences.

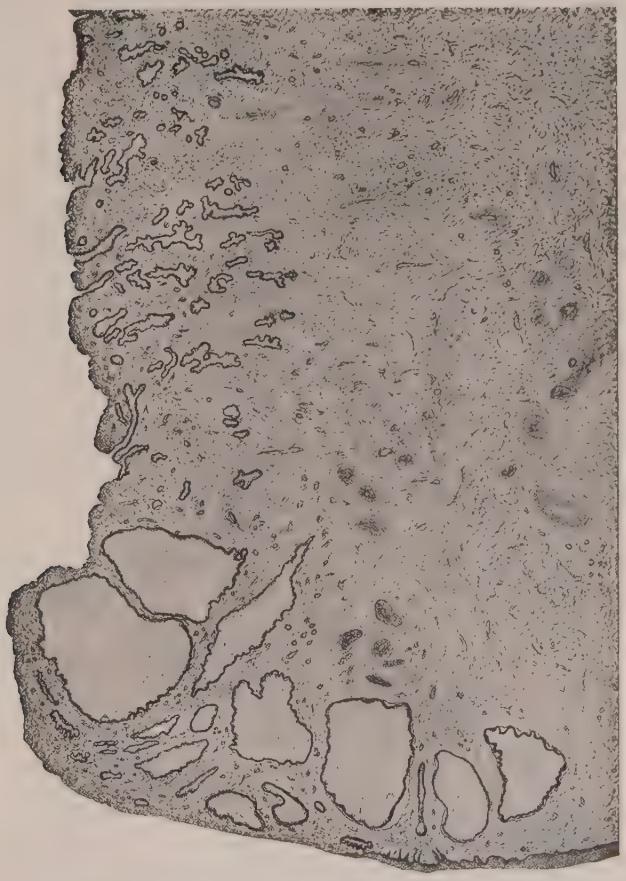


FIG. 616.—FIBROUS AND GLANDULAR HYPERPLASIA OF CERVIX UTERI.

The figure shows one side of the cervix in longitudinal section. The fibrous tissue of the cervix is very dense and the walls of the blood-vessels are thickened. There is hyperplasia of the glands of the cervical canal. The Nabothian glands are distended with clear, glairy fluid (ovula Nabothi). There is erosion of the epithelium at the os externum, and this, with the congestion of the small superficial vessels here, gave a rough red appearance to the os, suggestive of a malignant growth.

II. INFLAMMATION OF THE PREGNANT UTERUS.

The forms of inflammation which have just been described may also occur in the pregnant uterus. Metritis may lead to softening of the uterine wall, so that rupture takes place during labor. Perimetritis and parametritis produce adhesions and abscesses about the uterus.

Infectious Inflammation (Puerperal Fever).—Under normal conditions, for a week or more after delivery the inner surface of the still en-

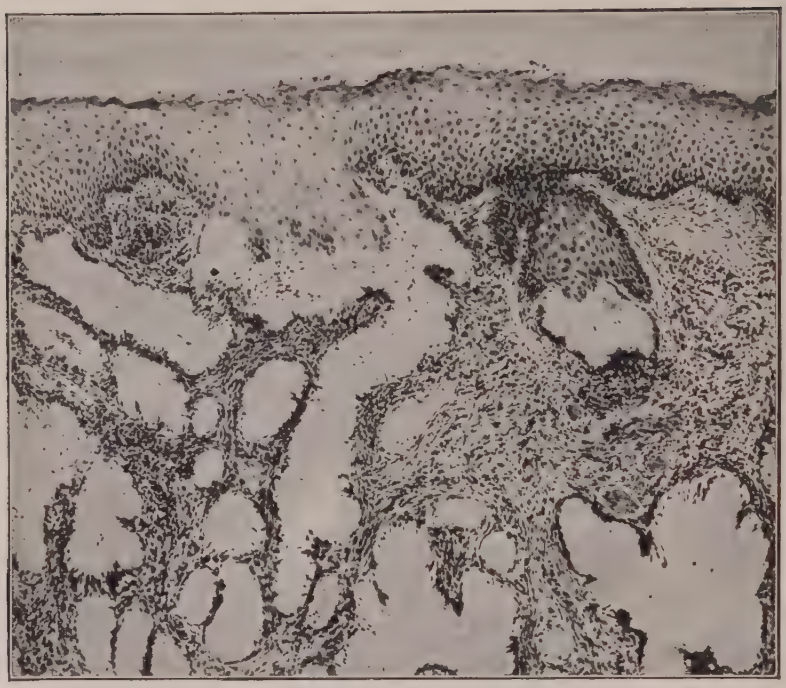


FIG. 617.—REPAIR IN CERVIX.
Showing downgrowth of epithelium into the mouths of the cervical glands during the repair of an endocervicitis glandularis.

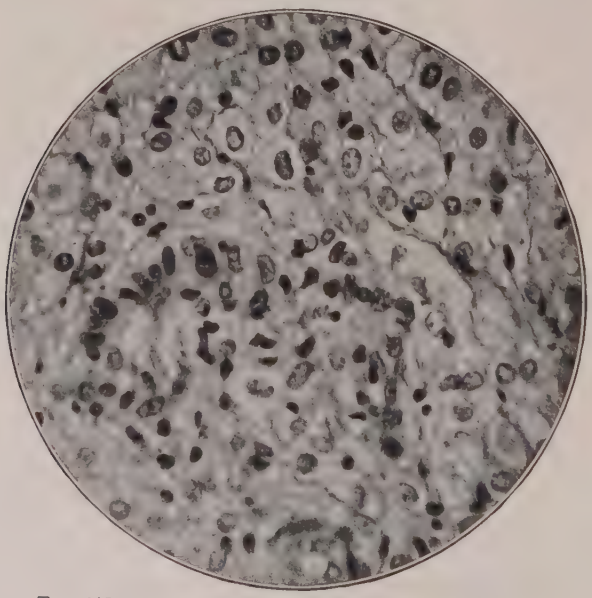


FIG. 618.—UNALTERED DECIDUA FROM EARLY PREGNANCY.

larged uterus is rough, especially at the insertion of the placenta, and covered with dark shreds of blood, remains of mucous membrane, and placenta. This condition should not be mistaken, as it sometimes is, for inflammation or gangrene.

As a result of injury to the uterus or vagina during or after delivery, and the action of bacteria which gain access to the tissues in this vulnerable state, the puerperal uterus is liable to become the seat of a series of severe and often destructive inflammatory and necrotic changes. These may be confined to the uterus; they may induce serious alterations in surrounding parts; or they may lead to an involvement of the peritoneum or to bacteriemia or pyemia and its accompanying lesions in the most

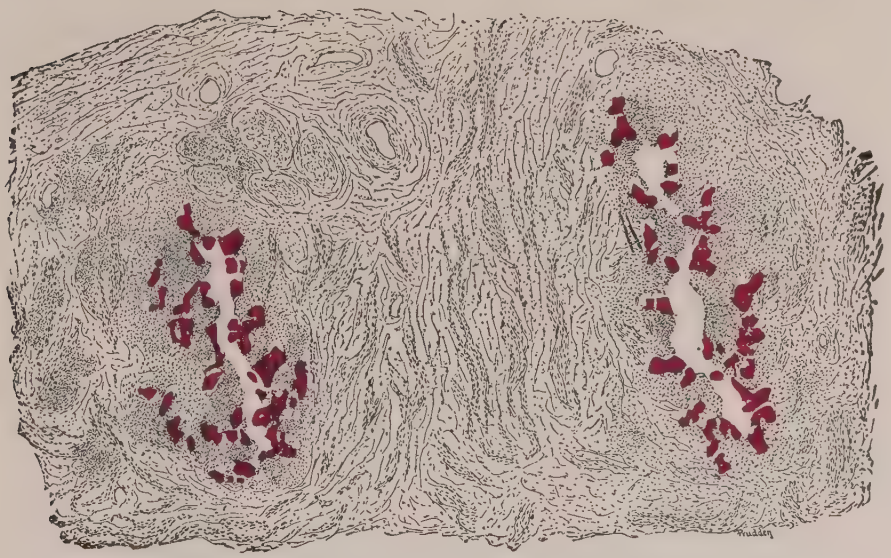


Fig. 619.—Uterine Phlebitis following Delivery; with Retained Placenta. Death nine days after delivery. Micrococci in the walls of the inflamed veins stained violet.

distant parts of the body. In some cases a more or less extensive gangrenous inflammation of the mucous membrane and the underlying parts may lead to the casting-off of larger and smaller shreds of necrotic tissue and the formation of deep and spreading ulcers, which may be accompanied by severe parametritis and fatal peritonitis. In other cases, the inflammation may be membranous and may affect the vagina, leading to necrosis, gangrene, ulceration, or peritonitis.

In connection with any of the above forms of inflammation, or without them, there may be thrombosis of the uterine sinuses, purulent inflammation of the veins, suppuration and abscess in the uterine wall, suppurative inflammation of the ovaries and tubes, and, owing to the generalization of the infectious material, metastatic abscesses in the lungs, spleen, kidneys, etc. Or acute pleurisy, ulcerative endocarditis, erysipelas, purulent inflammation of the joints, hyperplastic swelling of the spleen and lymph-nodes, thrombosis or thrombophlebitis of the saphe-

nous veins, etc., may follow. In some cases which rapidly pass to a fatal termination, the local lesions may be but slightly marked, and general alterations characteristic of pyemia, such as metastatic abscesses, etc., be entirely wanting. Death, in such cases, is due apparently to toxemia produced by the bacteria circulating in the blood (blood cultures).

Bacteria are usually present in the exudate, and in the lymph-vessels, veins, and inflamed tissue of the uterus (Fig. 619), and often in enormous quantities in the peritoneal exudation and in the metastatic inflammatory foci. Streptococcus pyogenes, the gonococcus, B. aërogenes capsulatus, and the colon bacillus are the most frequent excitants of the lesion.[1]

In general, it may be stated that puerperal infections begin as local processes. If the uterine reaction is sufficient and the virulence not excessive, the process remains localized as an endometritis or metritis. If the local resistance is overcome and invasion proceeds through the lymphatics and veins, more or less diffuse thrombophlebitic processes are set up, producing parametritic exudates (rarely fatal), progressive thrombophlebitis (pyemia, grave prognosis), and occasionally puerperal peritonitis by pure lymphatic extension (almost invariably fatal). Still more acute invasions rapidly overcome the local resistance, leave no evidence of infection in the periuterine connective tissues, lymph and venous channels, but flood the entire systemic vascular system with bacteria which rapidly multiply in the blood stream. Only a small number of patients with such infections recover.

TUMORS.

Simple **fibromata** of the uterus are almost unknown, the so-called fibromata being, in most cases, **myomata** or **fibromyomata.**

Lipomata have been described.[2]

Uterine Polypi are a common form of growth from the mucous membrane. Apparently they are intermediate between "polypoid endometrium," a simple endometrial hyperplasia, and true submucous fibromyomata which have become pedunculated. The presence of unstriped muscle fibers will decide the nature in favor of myoma. The polypi consist of more or less vascular connective-tissue stroma covered with epithelium. The surface may be smooth or villous. It may contain very numerous gland follicles, and then approaches the type of adenoma, or even of carcinoma (Fig. 620). The stroma may be loose and succulent and resemble mucous tissue, forming the so-called *mucous polypi.* The stroma may give rise to sarcoma or to myosarcoma. In any of these forms the blood-vessels may be abundant and dilated, forming telangiectatic or cavernous polypi. The adenomatous polypi may become cystic from dilatation of the gland follicles.

Polypi of the uterus may be multiple or single, small or large. In addition, numerous smaller and larger papillary outgrowths from the mucous membrane may occur from chronic stimulation of the uterine

[1] See *Wadsworth, A. B.*, Am. Jour. Obst., 1901, xliii, 439, for study of puerperal infection.
[2] *Ellis, A. G.*, Surg., Gynec., and Obst., 1906, iii, 658.

mucosa, probably ovarian in origin. Single polypi may grow from the mucosa of the body of the uterus or from the cervix, and hang by a long pedicle down into the vagina. The place of insertion of the pedicle is not the sole determining factor, but the character of the surface or glandular epithelium—in corporal polypi, low columnar in type; in cervical polypi, high columnar with clear protoplasm—must also be taken into consideration.

The large number of glandular structures in many of these chronically inflamed papillary and polypoid outgrowths often justifies the name of adenomatous hyperplasia of the mucous membrane or of adenomatous papillomata or polyps.

Polyps when projecting from the external os are subjected to trauma and to the irritating secretions of the vagina. Transformation of the

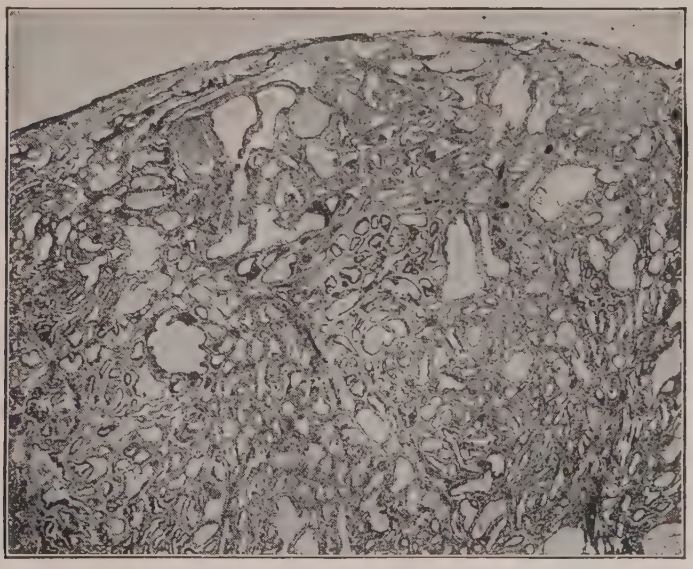


Fig. 620.—Polyp of Uterus.
Showing great abundance of glandular structures.

surface epithelium from the columnar to the squamous type,[1] invasion of gland lumina by the latter, as in erosion, and great proliferation of the epithelium are common. These changes do not signify malignancy.

Myomata.[2]—These tumors, whose characteristic structural elements are smooth muscle cells (Fig. 225), are the most common of uterine tumors and, while frequently of little practical importance, sometimes have serious consequences. They are especially common in negresses. They are most frequently composed of both muscular and fibrous tissue—*fibromyomata*—but the relative amount of the two kinds of tissue is

[1] *Oerie, R.*, Ztschr. f. Geburtsh. u. Gynäk., 1906, lvii, 384; *Hunziker, H.*, Frankfurt. Ztschr. f. Path., 1911, viii, 1; *v. Franqué, O.*, Ztschr. f. Geburtsh. u. Gynäk., 1911, lxix, 409.

[2] *Frankl, O.*, Arch. f. Gynäk., 1911, xcv, 269; *Kelly* and *Cullen*, Myomata of the Uterus, Philadelphia, 1909; and *Lockyer, C.*, Fibroids and Allied Tumors, London, 1918.

subject to great variation. Myomata are most apt to occur after puberty, during the period of sexual maturity. They may be single or multiple, small or of enormous size; they are usually sharply circumscribed, whitish or pink, dense and hard, or sometimes soft, and on section present interlacing bands or irregular masses of glistening tissue. Their usual situation is in connection with the body of the uterus, but they may occur in the cervix[1] or in the folds of the broad ligaments. According to their position, *subserous*, *submucous*, and *intramural* (*interstitial*) forms may be distinguished.

The *subserous myomata*, often multiple, grow from the outer layers of the uterus in the form of little nodules. As they increase in size they

Fig. 621.—Extramural Myomata.
Shows the uninvolved interior of the uterus containing a well-formed fetus.

may become separated from the uterine wall and remain attached only by a narrow pedicle or by a little connective tissue; or they may be entirely free from uterine connections, having formed new attachments to the adjacent or even more distant organs ("wandering" fibroids). They may work their way between the folds of the broad ligament until they are at some distance from their point of origin. The tumors may become very large, but still remain firmly attached to the uterus; this organ may then be drawn upward, the cervix and vagina being elongated and narrowed. The traction may be so great that the body of the uterus is entirely separated from the cervix. The bladder may also be drawn

[1] *Kolb, K.*, Ztschr. f. Geburtsh. u. Gynäk., 1910, lxvii, 399.

upward. Subserous myomata of considerable size may interfere but slightly with the function of the uterus (Fig. 621).

The *submucous myomata* grow from the inner muscular layers of the uterine wall, most frequently in the fundus. They may project into the uterine cavity and remain sessile or become pedunculated; the uterus dilates with the growth of the tumor, and its wall may become thickened. The submucous myomata are usually single, although there may exist at the same time subserous and intraparietal tumors. They are frequently soft, and if of large size and polypoid in form, may be extruded through the cervix and, in rare instances, drag down the fundus of the

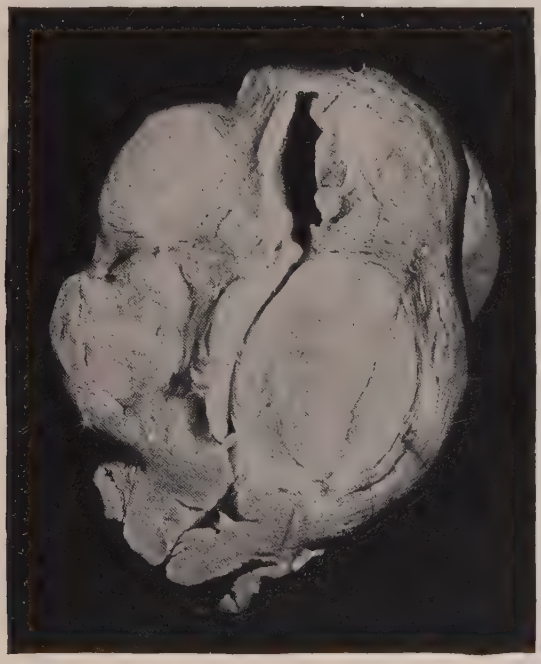


Fig. 622.—Intramural Myomata of Uterus.

uterus, producing inversion. The mucous membrane covering them may be atrophied or hyperemic, with dilated blood-vessels, and may thus give rise to severe and repeated hemorrhages. In some cases the pedicle of a tumor is destroyed and the growth is spontaneously expelled. Submucous polypi are especially vulnerable to changes in circulation producing hemorrhage, necrosis, and subsequent infection of the growth.

The *intramural myomata* grow in the substance of the uterine wall, but, if they attain large size, usually project beneath the serous or the mucous coat (Fig. 622). They are found in every part of the uterus, but are most frequent in the posterior wall.

The uterine musculature about a myoma is circumferentially arranged and lamellated. Except where the nutrient vessels enter the growth,

only a tenuous connection exists; hence, fibroids readily shell out of their "capsule."

The shape of the uterus is altered in a great variety of ways by the presence of these tumors; its cavity is narrowed, dilated, or misshapen; it undergoes flexion or version. The tumors may sink downward and become fixed in Douglas's cul-de-sac.

Myomata may undergo a variety of secondary alterations. A varying amount of *interstitial edema* may alter the size and consistence of the growth. The muscle fibers may undergo *fatty degeneration*, and the tumor may then diminish in size, or may even, it is said, be entirely destroyed. *Degeneration* of fibromyomata occurs most commonly in the puerperium as a result of the sudden cutting off of the blood supply. The most common degeneration is *hyaline*, which primarily affects the connective tissue of the growth, converting it into a structureless, faintly staining, glassy matrix (red, if stained with Van Gieson), between which the widely separated muscle bundles and fibers appear. Later, from lack of nutrition, the muscle also disappears. *Calcification* or *ossification* may occur, converting a part or the whole of the tumor into a stony mass. The intramural and submucous myomata may give rise to profuse hemorrhages; they may suppurate and become gangrenous.

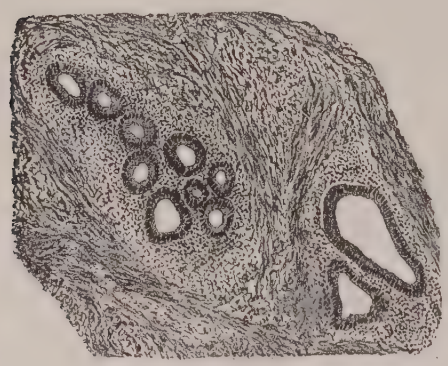


Fig. 623.—Adenomatous or Glandular Myoma of Uterus

Aseptic necrosis of myomata produces the so-called *carneous fibroid*, which on cross-section appears beefy, soft to semifluid, and in color from bright pink to deep red or violaceous. The histological details gradually disappear, a granular, diffusely staining débris marking the final stage.

Sometimes the tumors or circumscribed portions of them are very vascular, constituting the *telangiectatic* or *cavernous* variety. These tumors, which possess some of the characters of erectile tissue, may show sudden change in size from variation in the amount of blood which they contain. Larger and smaller cysts may develop within these tumors—*fibrocystic tumors*. These may be multiple and may communicate; they may be filled with a clear or bloody fluid. These cystic myomata sometimes reach an immense size and fill the abdominal cavity. The cysts may be lined with ciliated epithelium,[1] although this is the great exception. The majority of cystic cavities develop from aseptic necrosis of the tumor tissue, due to lack of blood supply, and, therefore, possess, no epithelial lining.

Myomata of the cervix[2] are moderately rare. They may grow as

[1] *Breus*, Ueber wahre Epithel führende Cystenbildung d. Uterusmyomen, Leipzig, 1894.
[2] *Kolb, K.*, Ztschr. f. Geburtsh. u. Gynäk., 1910, lxvii, 399.

polypi beneath the mucous coat, produce enlargement of the anterior or posterior lips, develop subperitoneally, elevating the uterus completely out of the pelvis, or grow outward into the abdominal cavity.

Myomata of the uterus, either subserous, intraparietal, or submucous, containing glandular structures of the type of those in the uterine mucosa, are of occasional occurrence (Fig. 623). These *glandular myomata* or *adenomyomata* are occasionally directly connected with the uterine mucous membrane, but are sometimes so distant and so entirely separated from it as to justify the conjecture that they are derived from some embryonal abnormality associated with the development of the Wolffian body.[1] Similar tumors have been described in the round ligament,[2] in the rectovaginal septum,[3] or at the umbilicus.[4] These embryonal rests are most commonly located at the tubal angles (v. Recklinghausen). Adenomyomata rarely have a well-defined capsule and, therefore, can not be "shelled out" as can fibromyomata.

Myomata evidence themselves mainly by an increase in size of the uterus and by producing hemorrhage (meno- and metrorrhagia). Pressure effects occur more often from small tumors in the pelvis or from impacted or subperitoneal growths than from large growths which rise into the peritoneal cavity. The mucous membrane overlying submucous tumors is usually thin and atrophic, but the neighboring mucosa, where not pressed upon, is usually hypertrophic. There is some evidence that myomata are due to excessive ovarian stimulation, which likewise produces the uterine hemorrhage commonly ascribed to the influence of the fibroid. Although fibroids may seriously complicate pregnancy, their influence in causing sterility is greatly overestimated. During the early months of pregnancy, the growth of fibroid tumors is usually rapid; but after the fifth month the rate generally diminishes. Sometimes the huge size attained by the tumor produces abortion before term is reached, or necessitates operation. Fibroids may produce dystocia. If the placenta is inserted upon a submucous fibroid, the afterbirth may remain adherent, as the thinned-out mucosa does not undergo a complete decidual reaction and the spongy layer of the endometrium is poorly developed. During the puerperium, fibroids are vulnerable to infection and often undergo degeneration.

Malignant Myomata.—Certain very cellular myomata have been known to produce metastases and evince an infiltrating growth. They may show no histological evidence of malignancy. Fortunately these tumors are rare.[5]

Von Recklinghausen's[6] description of adenomyoma of the uterus in 1896 first focussed attention upon the wide distribution of uterine mucosa. His assumption that the lesions could be ascribed to remnants of the

[1] *Cullen, T. S.*, Johns Hopkins Hosp. Rep., 1897, vi, 133 (bibl.); also monograph in Festschrift für Orth, Berlin, 1903.

[2] *Cullen, T. S.*, Bull. Johns Hopkins Hosp., 1898, ix, 142 (bibl.); *Blumer, G.*, Am. Jour. Obst., 1898, xxxvii, 37.

[3] *Jessup, D. S. D.*, Proc. New York Path. Soc., 1912, xii, 3.

[4] *Cullen, T. S.*, The Umbilicus and Its Diseases, Philadelphia, 1916.

[5] *Hoevels, K.*, Frankfurt. Ztschr. f. Path., 1911, viii, 477.

[6] *Von Recklinghausen*, Die Adenomyome und Cystadenome des Uterus und der Tubenwandung, Berlin, 1896.

Wolffian duct, though still held, has not obtained acceptance as a general explanation. Cullen somewhat later offered the explanation that such growths were displaced portions of the endometrium itself. There has gradually accumulated descriptions of similar collections of uterine mucous membrane, usually with smooth muscle fibres, in the sacro-uterine ligaments, the recto-vaginal ligaments, the pre-cervical connective tissue, the appendix, the vagina (Fig. 624), the tube, round ligaments, the pouch of Douglas and even hernial sacs. Later a group was described about the umbilicus, and finally Robert Mayer in 1903 found similar nodules in laparotomy scars (Fig. 625) and in the wall of the large intestine. Pick in 1905[1] recorded four cases of what he called endometrial adenoma of the ovary. Renewed interest in the matter was excited by Sampson,[2] who made a very complete study of the occurrence

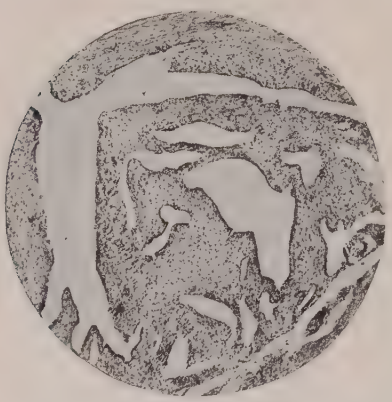


Fig. 624.—Decidual Reaction in Adenomyoma of Vaginal Wall. × 40.

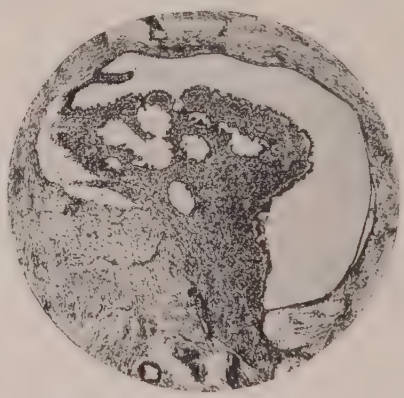


Fig. 625.—Adenomyoma in Laparotomy Scar. This Enlarged at Menstrual Period. × 30.

of such endometrial nodules and pointed out their importance in the production of the so-called chocolate or tar cysts of the ovary. Renewed study of the whole subject has made it evident that possibly three explanations underlie the occurrence of these lesions. It is probable that the peritoneum retains a certain embryonal capacity when irritated, inflamed, and especially under the hormonal stimulus of the ovary, to form glandular structures surrounded by a more or less cellular stroma. The adenomyomata in and in the proximity of the uterus are probably derived from displaced fragments of uterine or tubal mucous membrane, some possibly from the remnants of the primitive kidney and of Mueller's duct. A certain number of the superficial endometrioses are unquestionably produced, as Sampson believes, by transplantation of uterine or tubal mucosa.[3] Certainly the varieties growing in laparotomy wounds can only be explained by transplanting, either by sutures or in the process of sponging, pieces of mucous membrane in the site of the scar. Nevertheless, there are those who believe that fragments of

[1] *Pick*, Berl. klin. Woch., 1905, xlii, 502.
[2] *Sampson*, Surg., Gynec. and Obst., 1924, xxxviii, 287; Am. Jour. Obst., and Gynec., 1926, xii, 459.
[3] *Sampson*, Am. Jour. Path., 1927, iii, 93.

peritoneal tissue have been sewn into the wound and there proliferate and form endometrium. If such is the case, why do they not occur in laparotomy scars in men? Hence the invocation of an ovarian hormonal stimulation. It has also been shown that uterine mucosa can be experimentally transplanted in animals and that nodules resembling those seen clinically in the human being are produced.[1]

The clinical interest in these nodules is two fold: one the fact that, being fragments of endometrium, they respond to the hormonic stimulation of the ovary at the time of menstruation and therefore become swollen, painful and hemorrhagic at that time. Figure 625 shows such a nodule in an abdominal scar which exhibited these symptoms, and the fact that menstrual blood has been set free in the lumen of the cyst is shown by the phagocytic cells nearly filled with blood pigment. During pregnancy decidual changes can be seen in such endometrial fragments (Fig. 624). The other reason for clinical interest is the occurrence of malignant tumors presumably arising in these endometrial transplants. This is extremely rare, but has been occasionally observed.

Sarcomata of the uterus[2] occur most frequently in circumscribed areas, usually developing in an intramural myoma. Much more rarely do they appear as a diffuse involvement of the wall of a uterus of normal musculature. Endometrial sarcomata are the least frequent type seen.

The circumscribed mural growths usually tend to extend toward the uterine cavity and may become polypoid. A rarer development is toward the peritoneal surface which they may penetrate and then rapidly involve the vessels and neighboring tissues of the abdominal cavity. The diffuse mural growths may also assume a polypoid form and fill the dilated uterine cavity with closely packed masses. Macroscopically the sarcoma tissue differs considerably in appearance from the normal uterine musculature, though very small growths may escape detection. Usually the cut section is duller than the uterine wall and has less luster. It is also softer and putty-like. The color is grayish or yellowish and punctate hemorrhages are apt to be present.

Secondary changes are frequent resulting from the thrombosis of the blood sinuses in the tumor and consequent necrosis of the tributary structures. The cells become fatty, necrose and are absorbed, giving rise to liquefaction and cyst formation. Such necrosis may be so extensive as to leave only a shell of intact tumor tissue nourished by the large blood vessels from the surrounding healthy structure. Microscopically the early tumors are extremely difficult to differentiate from the more cellular parts of a fibromyoma. The fully developed tumors, however, are easy of diagnosis. They are usually of two types, one—and the most frequent—a pure spindle-cell sarcoma, showing abundant mitoses, the other, the myosarcoma, having a polymorphous structure (Fig. 626), showing great variation in the size of the nuclei and cell bodies with fewer mitoses. Giant cells may even be present.

[1] *Stilling, H.*, Zeigler's Beiträge, 1910, xlvii, 499; *Hesselberg, Kerwin* and *Loeb*, J. Med. Res., 1918, xxxviii, 11; *Jacobson*, Arch. Path. and Lab. Med., 1926, i, 169.

[2] For references on the occurrence of sarcomatous changes in myomata, see *Evans*, Surg. Gyn. and Obst., 1920, xxx, 225.

The round-cell sarcomata or lymphosarcomata of the uterus are rare. In the first type the cells are much larger than a lymphocyte and are often mingled with muscle cells or growing connective tissue cells, spindle in shape. Their origin is possibly from the reticular cells surrounding the blood vessels. The morphology of the lymphosarcomata does not differ from that of similar growths elsewhere.

Fig. 626.—Myosarcoma of Uterus.

Metastasis of the sarcomata takes place through the blood vessels and therefore the lungs are frequently involved, but in general uterine sarcoma is not a highly malignant type and the results of hysterectomy are quite as good as those of carcinoma. Sarcoma of the uterus is a rather rare disease, its frequency being only about one-fortieth of that of carcinoma of the organ. The statistics of the frequency of sarcomatous changes occurring in myomata vary a great deal, probably in only one per cent. of the benign tumors do sarcomata develop. The reported ten and twelve per cent. frequencies are probably due to the mistaking of very cellular fibromyomata for sarcomata. The disease occurs most often between the ages of forty-five and fifty.

Sarcoma of the cervix is a very rare form. It may appear as a cauliflower growth indistinguishable from a sarcoma grossly and sometimes very closely resembling carcinoma microscopically (Fig. 627) or as a diffuse enlargement of the cervix. This type is apt to involve the vaginal wall and is more malignant than the sarcoma of the body.

Sarcoma botryoides has been previously described. *Carcinosarcoma*,[1] *angiosarcoma*,[2] *chondrosarcoma*,[3] *and ganglioma*[4] occur rarely.

[1] *Forssner, H.*, Arch. f. Gynäk., 1909, lxxxvii, 445.

[2] *Polano, O.*, Ztschr. f. Geburtsh. u. Gynäk., 1910, lxvii, 413.

[3] *Gebhard, C.*, Ztschr. f. Geburtsh. u. Gynäk., 1902, xlviii, 111; and *Penkert, M.*, Beitr. z. Geburtsh. u. Gynäk., 1905, ix, 488.

[4] *Pick, L.*, Berl. klin. Wchnschr., 1912, xlix, 16.

Carcinomata.[1]—From the descriptive aspect, carcinoma of the uterus is advantageously divided into tumors of the vaginal portion of the cervix, tumors of the cervical canal, and tumors of the uterine cavity (corpus carcinoma). This division also corresponds most closely to clinical considerations.

1. *Carcinoma of the vaginal portion of the cervix* most probably always originates in the immediate vicinity of the external os, in most cases from erosions or from lacerations. Multiparæ are more subject to this form of cancer than nulliparæ. The tumor may assume cauliflower or papillary form, appear as an indurated invasive ulcer, or begin as a subepithelial diffuse thickening of part of the cervix. Necrosis, subsequent

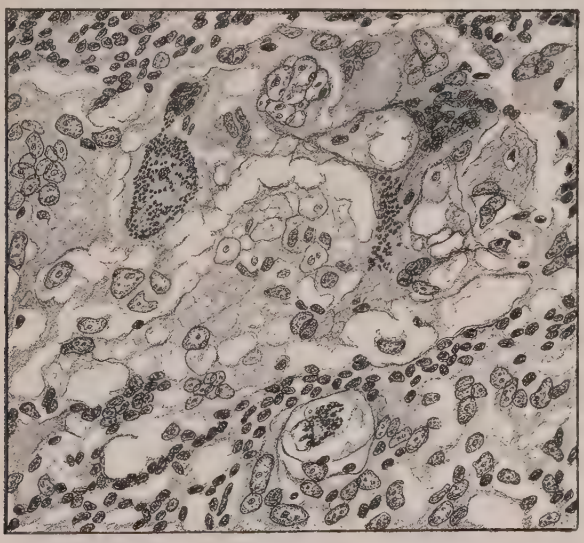


Fig. 627.—Epithelioma of Cervix Resembling Sarcoma.

infection, bleeding, and foul-smelling discharge are early symptoms. Extension to the vaginal vault, vagina, and parametria, and involvement of the bladder and rectum regularly occur. The cervical canal is eventually invaded, and nodules, apparently independent, may be found in the vagina and uterine musculature, though serial section proves them to be direct lymphatic extensions.

2. *Carcinoma of the cervical canal* may be diffuse or nodular. The vaginal portion may appear normal although the entire cervical canal is involved. Hemorrhage and foul discharge are early symptoms. This form of tumor is very malignant because the thin shell of cervix permits early extension into the parametria.

3. *Carcinoma of the corpus uteri* begins most frequently as a polypoid growth in one of the tubal angles; a diffuse involvement of the uterine cavity is less common. Clinically, this is the least malignant variety of uterine carcinomata,[2] because it remains localized for a long period.

[1] *Cullen, T. S.*, Cancer of the Uterus, New York, 1900.
[2] *Ladinski, L. J.*, Surg., Gynec., and Obst., 1915, xx, 325; *Boldt, H. J.*, ibid., p. 313.

Gross Appearance.—Uterine carcinomata are whitish to pinkish, friable growths, which on gross section show infiltration and substitution of surrounding structures and a soft granular surface from which "cancer juice" can be wiped away with the knife edge.

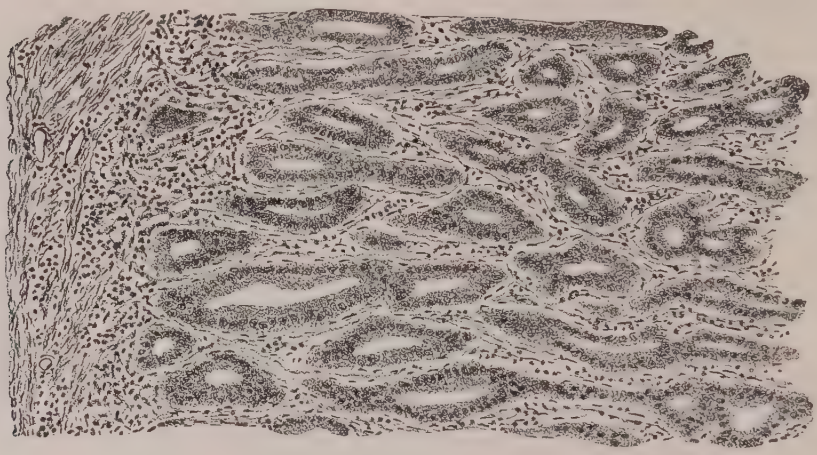


FIG. 628.—ADENOCARCINOMA OF UTERUS.

Extension.—Uterine cancer is of frequent occurrence and, although a disease of early middle life, has been reported in young women (eighteen years). Early stages are rarely recognized. In the operable cases the parametria are found involved in more than 50 per cent. Involvement

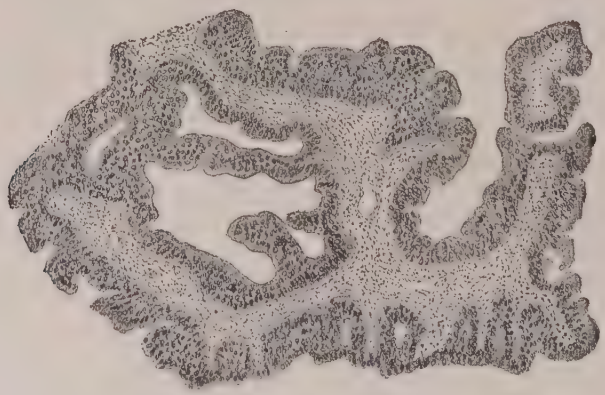


FIG. 629.—ADENOCARCINOMA OF UTERUS.
Showing a small portion of a glandular and papillary growth.

of the lymphatic nodes is also of frequent occurrence, even in operable cases (more than 20 per cent.), the parametrial, iliac, hypogastric, and aortic nodes being affected.

Invasion.—As previously mentioned, neighboring structures are invaded by continuous or discontinuous growth. The vagina, bladder,

and rectum may be converted into a single cancerous cloaca. The parametrial outgrowths often surround the ureters, causing stenosis, hydroureter, hydronephrosis, and pyonephrosis. The ureteral wall is highly resistant to the tumor.

Metastases to other organs are of late occurrence. In order of frequency, the lung, liver, kidney, and ovary are involved.

Histology.—An almost unbroken series can be traced from apparently adenomatous growths (all of which are malignant) to squamous-cell carcinoma. In many growths different areas show a different morphology.

"Malignant Adenoma" and Adenocarcinoma.—This variety is most characteristic of corpus carcinoma, although very malignant tumors of this type are frequently found within the cervical canal. Parts of the section may consist of an inextricable network of irregular, closely crowded glands lined with a single layer of epithelium (Fig. 628); while in other parts the gland

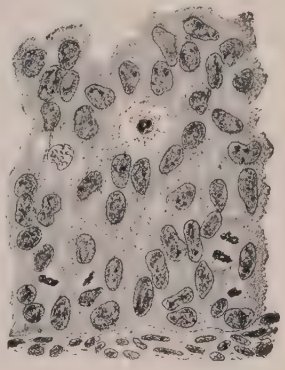


FIG. 630.—ADENOCARCINOMA OF THE UTERUS.

Showing a small portion of the epithelium in Fig. 629 more highly magnified. Mitotic figures are seen in the deeper layers.

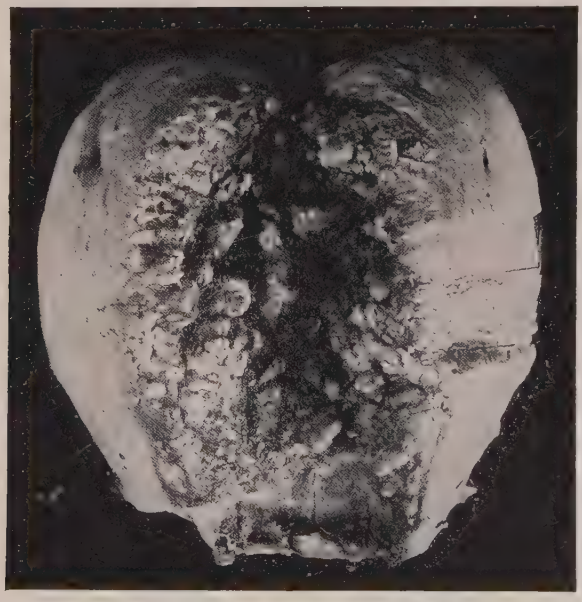


FIG. 631.—ADENOCARCINOMA OF UTERUS.

Showing the gross appearance of the interior of the uterus with an adenocarcinomatous involvement of the entire mucosa.

epithelium will be found arranged in several layers, and will show great diversity in size, shape, and nuclear dimensions (Fig. 629 and

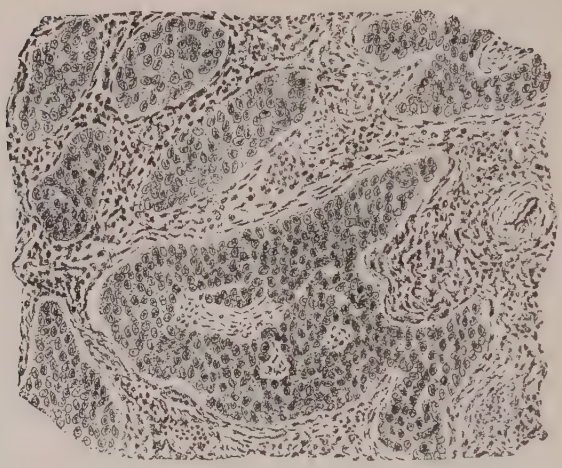


FIG. 632.—CARCINOMA OF UTERUS. Medullary type.

FIG. 633.—CARCINOMA OF CERVIX UTERI.
The infiltrating and ulcerating type.

630). Invasion and destruction of the uterine wall, also, may be apparent (Fig. 631). Toward the surface a gradual transition into the squamous type is occasionally found.

Medullary carcinoma appears in an alveolar distribution (Fig. 632), forming "solid" carcinoma if the alveoli are large, "scirrhous" carcinoma if the connective tissue predominates. Pseudoglandular forms are produced by central necrosis in the alveoli, though intermingling of areas of true glandular (adenomatous) configuration may be noted. The cells are closely crowded; the cell bodies are small and not plainly outlined. At the periphery, extension into the lymph-channels, or between the muscle or connective-tissue bundles, shows the invasive properties of the growth.

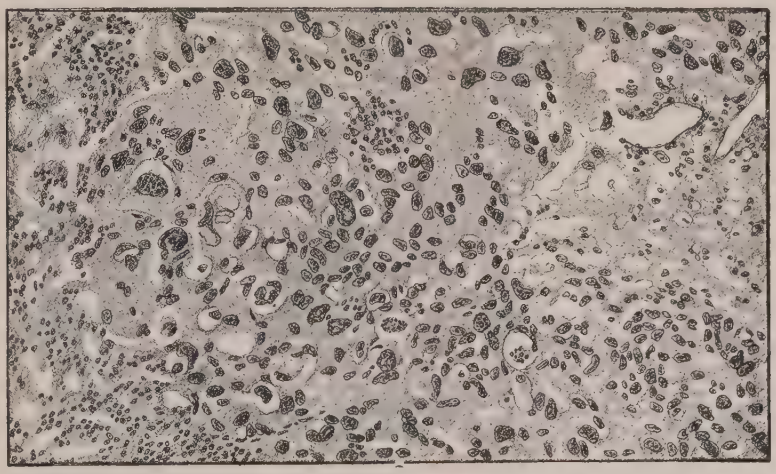


Fig. 634.—Epithelioma of Cervix. Syncytial Type.

Squamous-cell carcinoma may be highly differentiated, resembling the normal squamous epithelium of the vaginal portion of the cervix, but distinguished by the absence of regular arrangement into three layers, by invasion downward of finger-like processes projecting into the connective tissue and glands (Fig. 633), and by the marked round-cell zone of reaction which surrounds its margins. In other areas, the cells show marked deviations from the normal, nuclear irregularity, polymorphism, giant-cell or even syncytial complexes appearing (Fig. 634). Prickle cells and pearl formations are of common occurrence (Fig. 635); necrosis, hemorrhages, or hyaline degeneration of some areas may be noted. Types of growth resembling basal-cell carcinoma have been described.

Multiple carcinomata, for example, appearing simultaneously in the corpus and on the vaginal portion, have been noted. Unless the possibility of lymphatic extension is excluded by serial sections between the sites of the tumors, such cases should not be classed as authentic, even if the tumors are dissimilar in type.

Carcinoma and fibroid or carcinoma invading a fibroid have been reported. The coincidence may be accidental.

Carcinoma and tuberculosis are occasionally found in the same uterus.

Carcinoma and Pregnancy.—The carcinoma is always of the cervix, usually of the vaginal portion. Gestation appears to favor the rapid extension of the growth. Infection, hemorrhage, and, during labor, dystocia, may develop.

Metastatic carcinoma of the uterus is rare. It is noted most frequently as a sequel to ovarian cancer. Next in order of frequency are those

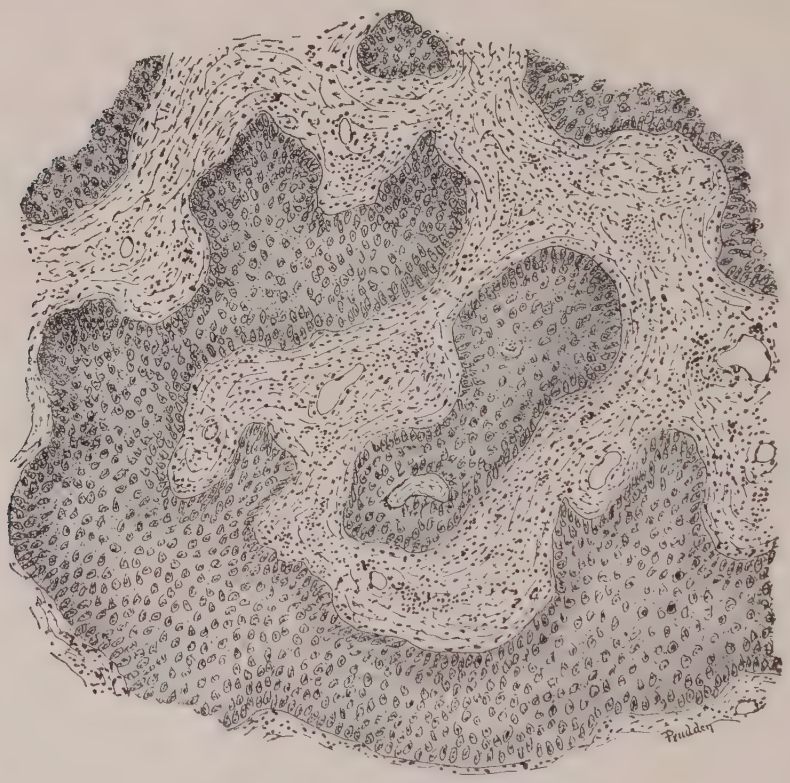


FIG. 635.—CARCINOMA (EPITHELIOMA) OF UTERUS.
Showing ramifying epithelial cell masses.

secondary to gastric, gall-bladder, breast, and rectal cancers. The metastatic nodules are found most often in the uterine musculature and when small are often situated in the lymph-channels.

Chorionepithelioma of Pregnancy. (Chorioma.)

Malignant tumors derived from chorionic villi or from some abnormal form of these, as hydatid moles (page 974), and composed of cells more

or less closely resembling the various types of chorionic epithelium, are known as *chorionepitheliomata of pregnancy.*[1]

Characters of the Chorionic Villi.—The chorionic villi consist of a vascular mucoid connective-tissue framework which is covered with two layers of epithelial cells of fetal origin. The inner layer is formed in general of a single layer of sharply defined, polyhedral, transparent cells with oval nuclei. These cells contain glycogen, and are called *Langhans' cells.* The outer layer is composed of a cell mass with many nuclei of

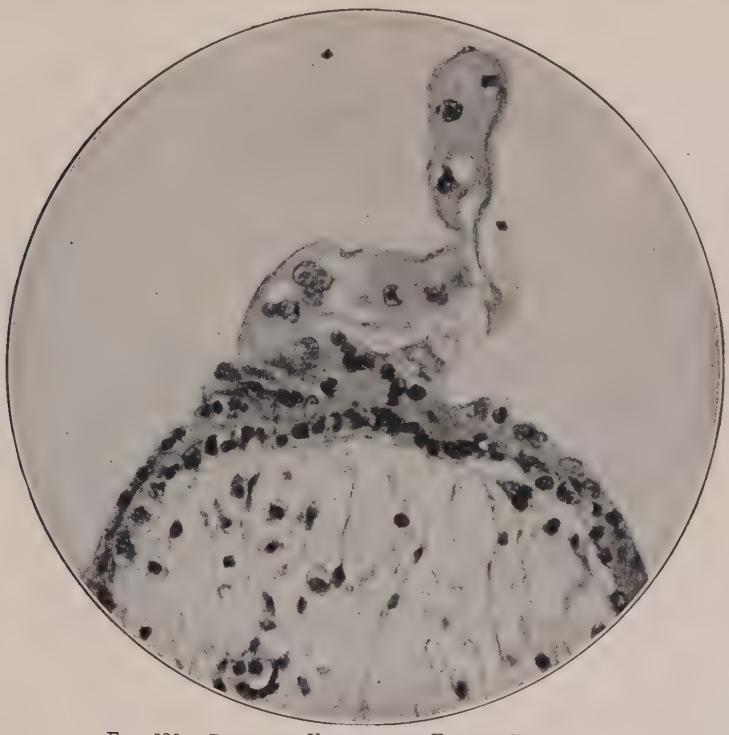


FIG. 636.—CHORIONIC VILLUS FROM ECTOPIC PREGNANCY.

various shapes embedded in a deeply staining vacuolated protoplasm, the whole resembling masses of giant cells, as no cell boundaries exist. This outer layer of cells is called the *syncytium,* and from it small protoplasmic, bud-like processes— *syncytial buds*—project (Fig. 636). The outer surface, in appropriately fixed specimens, shows a margin covered with rods resembling cilia. In the later periods of pregnancy the cell layers are, as a rule, less distinct than at an earlier time, the Langhans' type disappearing. The cells covering chorionic villi, by virtue of a proteolytic ferment, penetrate the maternal decidua, mingling with its

[1] This specific designation is necessary because tumors of similar morphological characters, but differently derived, occur in non-pregnant women, in the testicle, and elsewhere as parts of teratomata. For a summary of these tumors, with a study of new cases and bibl., see *Frank*, Jour. Am. Med. Assn., 1906, xlvi, 248: *Risel, W.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907, xi, 928: and *Woglom, W. H.*, St. Luke's Hospital Medical and Surgical Rep., iv, 1917, p. 188.

cells, and may invade the structures of the uterine wall. Certain of the covering cells of the chorionic villi have remarkable powers of penetrating the maternal tissues, their invasion being secured, apparently, through this lytic action. These are called *chorionic wandering cells*. They may erode blood-vessels, causing hemorrhage and thrombosis, and may enter the maternal circulation and be carried as emboli into the viscera[1]—liver, lungs, etc.—usually without the production of disturbing symptoms.

It is cells of these three types—Langhans' cells, syncytium, and chorionic wandering cells—invading the tissues of the uterus, from which

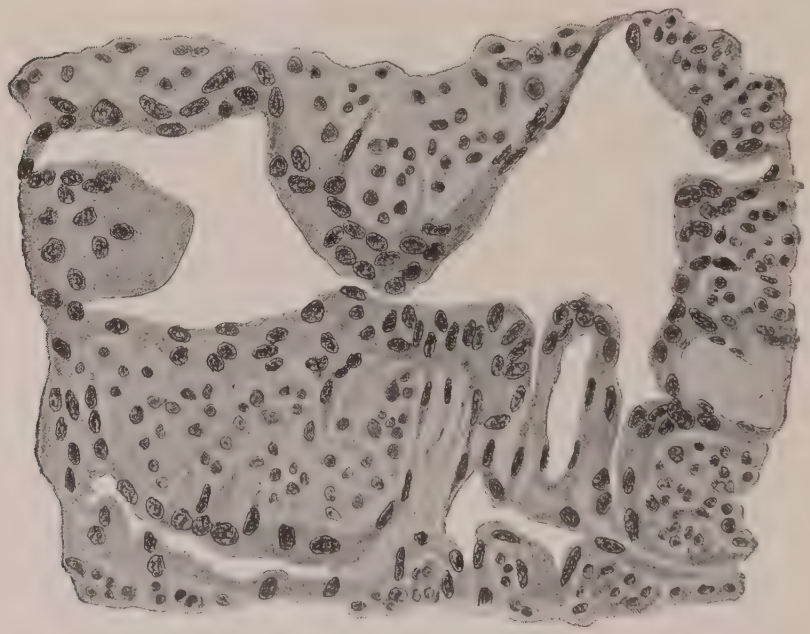


FIG. 637.—CHORIONEPITHELIOMA.
A mediastinal tumor showing the syncytial cells and the Langhans' cells in characteristic relationship to each other.

they directly derive their nourishment, without the development of a special stroma, as is the case of most tumors, that give a malignant character to chorionepitheliomata when they have become freed from the restraints of normal growth.

Chorionepitheliomata of the uterus form polypoid or nodular tumors, most commonly at the placental site, usually appearing a short time after the expulsion of a mole or after an abortion. Cases are on record where a long period of latency (five years) intervened between the pregnancy and tumor formation. The tumors are red to purplish, friable, and in-

[1] For a study of embolism of chorionic cells, see *Schmorl*, Verhandl. d. deutsch. path. Gesellsch 1904, viii, 39; Zentralbl. f. Gynäk., 1905, xxix, 129; and *Schotten, B.*, and *Veit, J.*, Ztschr. f. Geburtsh. u. Gynäk., 1903, xlix, 210.

filtrating. They are often multiple. On section, blood clots are noted as integral parts of the tumors.

Ectopic chorionepithelioma is a rare variety, in which the tumor first occurs at a distance from a possible pregnancy site (*i.e.*, uterus or tube), and is evidently due to the transportation of fetal elements by the blood stream, the embolus proliferating, the placental originator being expelled from the uterus.

Regression of chorionepithelioma has been observed.[1] Both primary tumors and metastases may regress; and cures have resulted after incomplete removal. On the whole, while chorionepithelioma is one of the most malignant varieties of tumors known, no histological distinctions between malignant and less malignant varieties have been discovered.

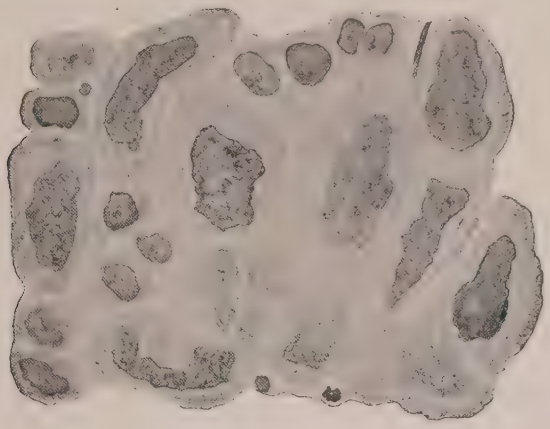


FIG. 638.—LARGE CELLS FROM CHORIONEPITHELIOMA OF UTERUS.
Vaginal curettings.

In typical chorionepithelioma of pregnancy (Fig. 637) two characteristic types of cells are distinguishable: the first, large polynuclear cells or cell masses—syncytial masses—appearing in irregular multinuclear strands or branching protoplasmic structures, and the second, more transparent, sharply circumscribed, polyhedral cells with single oval nuclei, with glycogen-containing protoplasm. These tumors regularly contain free blood and fibrin, and the stroma is largely made up of the tissue which they invade.

In many instances these tumors are less typical in structure, departing more from the character of the chorionepithelium. The delicately outlined transparent cells may be absent; the syncytial masses may fail; the whole growth may be made up of irregularly shaped cells of various sizes with nuclei varying in size but often very large (Fig. 638). The cells are sometimes multinuclear. Chorionepithelioma, therefore, may be divided into *typical* and *atypical*, the latter including those tumors in which syncytium or chorionic wandering cells predominate almost to the exclusion of the other types.

[1] *Teacher, J. H.*, Jour. Path. and Bacteriol., 1908, xii, 487.

Chorionepitheliomata were at first regarded as sarcomata, but are now known to be derived from cells of the chorionic villi which are derived from fetal ectoderm.

The development of these tumors most often follows hydatid mole. In the malignant types there may be invasion of the wall of the uterus and the pelvis (Fig. 639). Vaginal metastases are common and develop early, and there may be general metastasis with secondary tumors, most often in the lungs and liver. They may develop as a sequel to ectopic gestation (tubal chorionepitheliomata), but this is rare.[1]

Chorionepithelioma of the uterus produces severe hemorrhages, fever, and cachexia. On curettage, suspicious material may be obtained.

FIG. 639.—INVASION OF UTERINE SINUS BY CHORIONEPITHELIOMA.

Quite characteristic is the fact that if the first curettage is inconclusive, another curettage, practised within a few weeks, will evacuate even more placenta-like material.

Chorionepithelioma with Teratoma.

Several cases are recorded in which females whose age or condition precluded the possibility of pregnancy have developed tumors of the ovary having the characters of the chorionepitheliomata. These, it is believed, are all instances in which teratomata furnished the embryonal ectodermal tissues in which the tumors originated. Similarly, the so-called chorionepitheliomata of the testicle (Fig. 717), of which several cases have been described, are derived from teratomata. (See pages 403 and 1044.)

[1] For a study of clinical and microscopical variations of these tumors, with suggestions for diagnosis, see *Frank, R. T.*, N. Y. Med. Jour., 1906, lxxxiii, 793.

PARASITES.

Echinococcus has been found in the body and neck of the uterus, and may rupture into the peritoneal cavity or into the vagina.

The Placenta.

Aside from the variations from the normal in size, shape, and position, for a description of which we refer to the works on obstetrics, we may mention here briefly some of the more important structural changes which the placenta may undergo.

DEGENERATION.

Fatty Degeneration and calcification of the placental tissue are of not infrequent occurrence. A certain degree of fatty degeneration and calcification is physiological as the end of pregnancy is approached.

HEMORRHAGE.

This may occur either on the maternal surface in the decidua, or between the fetal surface and the membranes, or in the substance of the placenta. The latter form of hemorrhage constitutes the true *placental apoplexy*. This may occur as the result of rupture of a placental sinus. The placental tissue is crowded apart, and a blood-clot, often infiltrating the parenchyma, is formed. This may lead to abortion, or the blood may undergo disintegration and absorption and its place be occupied by a cicatrix. The placental tissue in its vicinity may undergo fatty degeneration. Under other conditions, without evidence of rupture of the vessels, the placental tissue may become infiltrated with blood in the form of an infarction. In this, degenerative changes similar to the above may occur, leading to fibrous induration of the placenta.

Placental hemorrhage varies in dignity depending upon its effect on the embryo. If the embryo is destroyed in the early months and expulsion of the chorion does not take place, a "placental mole" may develop. If hemorrhage occurs in the later months of pregnancy, maternal death may result from loss of blood. Hemorrhage occurs most commonly in patients with a high degree of albuminuria and is almost invariably accompanied by diffuse disintegration of the uterine musculature.

The so-called "*infarctions*" of the placenta vary in size, appearance, structure, and origin. They are most frequently due to an endarteritis of the vessels of the chorionic villi. They appear to be of little significance when of moderate size. Microscopically they consist of necrotic, poorly staining villi surrounded by fibrin.

INFLAMMATION. (Placentitis.)

Suppurative Inflammation of the placenta, with the formation of abscesses, is of rare occurrence as the result of injury.

[1] For a study of the placenta, normal and pathological, see *Eden, T. W.*, Jour. Path. and Bacteriol., 1896, iii, 449; 1897, iv. 265 (bibl.).

Chronic Indurative Inflammation of the placenta may result in the formation of circumscribed masses of cellular and loose, or dense and cicatricial, connective tissue, or in a diffuse formation of connective tissue which may interfere with the nutrition of the fetus and cause abortion. The new-formed connective tissue may undergo fatty degeneration or calcification.

In another class of cases, the new connective tissue is formed mainly in the walls of the vessels, particularly the arteries. This may occur in circumscribed portions of the vessels, leading to nodular growths around the arteries, or it may occur extensively along the various ramifications of the vessels, converting them into thick fibrous cords. The change is primarily in the adventitia, but all the coats of the vessel may become involved, leading to more or less complete obliteration of the lumen.

Various proliferative and indurative changes in the placenta must be ascribed to **syphilitic inflammation.** On the other hand, the placenta may show no alteration in this condition. Suspicion of syphilis is aroused by a disproportionately large placenta. The villi may be overplump and closely packed, and the intervillous space obliterated. Spirochetes have been found in the placenta, but are more readily discovered in the fetal lungs, liver, etc. Endarteritis of the vessels of the villi is not characteristic, though it may be suggestive, of lues.

Tuberculous Inflammation of the placenta may occur in connection with other tuberculous processes in the mother.

TUMORS.

Moles.—Under various conditions interfering with its nutrition the fetus may die and be cast off. The placenta and membranes, if retained,

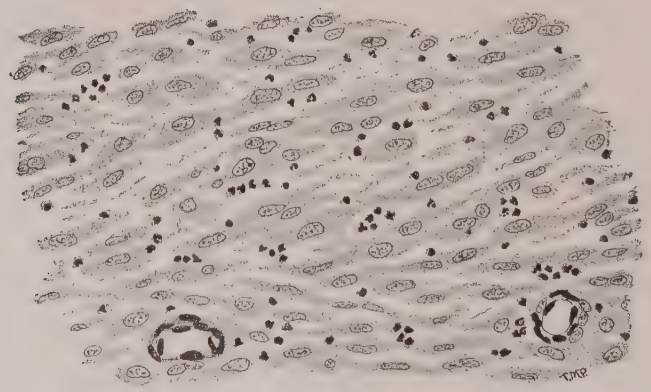


Fig. 640.—Fragment of Macerated and Edematous Decidua in Curettings from the Uterus.

may then dry, forming a fibrous or fleshy or bloody mass—*fibrous mole; fleshy mole; bloody mole.* These are not genuine tumors.

Placental Polyps.—Not infrequently, especially after abortions, portions of the placenta (Fig. 640) remain attached in the uterus and may undergo various phases of hyperplasia forming polypoid outgrowths

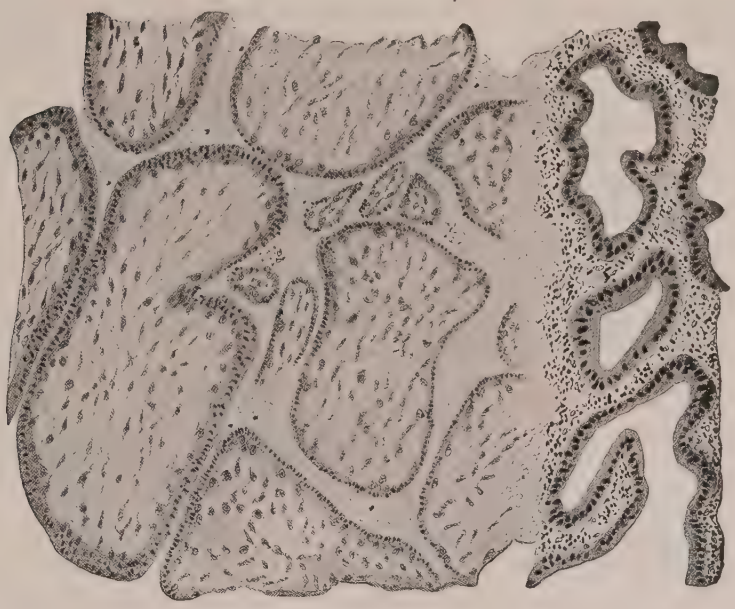


FIG. 641.—CURETTINGS FROM UTERINE CAVITY SHOWING PORTION OF RETAINED PLACENTA, AND OF THE MUCOUS MEMBRANE SHOWING GLANDULAR HYPERPLASIA.

FIG. 642.—HYDATID MOLE.
Showing a small portion of the mass.

or diffuse thickening of the mucous membrane, resembling some of the forms of moles in character. This condition is often associated with persistence of the decidual reaction, and curettings of the uterus may then show both placental structures and glandular hyperplasia of the mucous membrane with marked decidual characters (Fig. 641).

Sometimes, however, the placenta, or some part of it, is transformed into an irregular mass of rounded pink or colorless transparent or translucent bodies, from two to ten millimeters in diameter—*hydatid moles* (Fig. 642 and 643). These bodies, macroscopically resembling bunches of grapes in which the individual grapes are attached to one another directly or by tenuous stalks, consist of loose vascular connective tissue resembling mucous tissue, and are covered with very actively proliferating

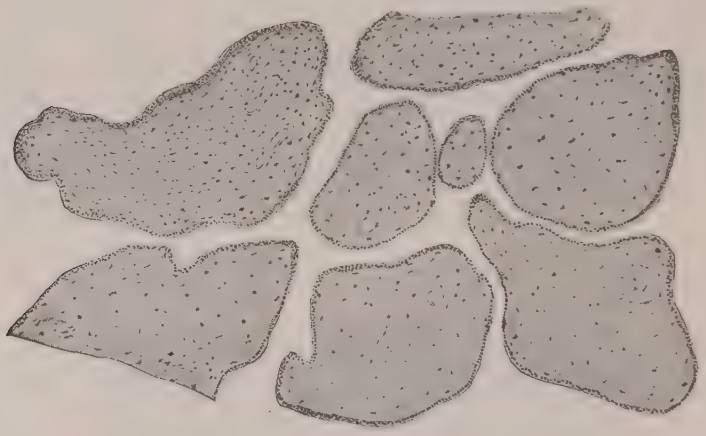


FIG. 643.—HYDATID MOLE.
Section of a small portion showing mucous and slightly fibrous tissue covered with a layer of epithelial cells.

chorionic epithelium. The cause of this transformation of the placenta is unknown. It may be cast off with the fetus or there may be no trace of the embryo. The hydatid mole may remain after the fetus is discharged, and through the growth of the chorionic epithelium may give rise to chorionepithelioma[1] (page 966), or to chorionepithelial emboli in various parts of the body,[2] with metastatic growths having the characters of hydatid moles.[3] An hydatid may destroy the fetus; a live fetus and a partly hydatid placenta may occur; in twin pregnancy one twin may be represented by the hydatid. Clinically, the uterus increases far beyond the corresponding size for the same month of pregnancy. A peculiar, often transient enlargement of the ovaries, lutein cystic degeneration, is not infrequently noted in connection with hydatid mole and chorionepithelioma.

[1] See *Pick, L.*, Berl. klin. Wchnschr., 1897, xxxiv, 1069, 1097.

[2] See *Schmorl*, Verhandl. d. deutsch. Naturf. u. Aerzte, 1897, ii, part 2, 21, 111; also *ibid.*, Verhandl. d. deutsch. path. Gesellsch., 1904, viii, 94.

[3] For pathology of hydatid mole and chorionepithelioma, see *Frank, R. T.*, Am. Jour. Obst., 1911, lxiv, 435.

Cysts of the placenta are of occasional occurrence; their origin is in many cases obscure.[1]

The Ovaries.

Malformations.

One or both ovaries may be absent, the other organs of generation also being absent or undeveloped; or they may be only partially developed. There may be accessory ovaries or even a third ovary. Absence or arrest of development of one ovary occasionally occurs in otherwise well-formed individuals, and is sometimes accompanied by a low position of the kidney on the same side. The ovaries may pass into the inguinal canal or into the labia majora, and may remain fixed there through life. Less frequently they are found in the crural canal or in the foramen ovale.

Changes in Size and Position.

The ovaries may become larger than normal through chronic inflammation or through the formation of cysts and tumors. In old age they become atrophied, the Graafian follicles disappearing and the organ shrivelling into a small, irregular, fibrous body. Atrophy may be produced by chronic inflammation or by unknown causes. As the result of the maturing and rupture of the Graafian follicles, with or without pregnancy, the surface of the ovary, which before puberty is smooth, may become roughened by irregular cicatricial depressions; in extreme cases, so-called "gyrate" ovaries result with incisures resembling the convolutions of the brain.

In adult life the ovaries may pass as herniæ into the inguinal or crural canal, the foramen ovale, or the umbilicus. Their position in the abdomen may be changed by the pressure of tumors, the traction of false membranes, etc. This may occur in enlarged ovaries or in those of normal size, and by the compression of the veins may lead to congestion and chronic inflammation of the organs.

HYPEREMIA AND HEMORRHAGE.

Aside from the normal hyperemia of the ovaries during various sexual functions, the vessels may be congested in inflammation, in displacements with interference with the venous circulation, in certain diseases of the heart, etc., and this congestion may be followed by interstitial changes. Such changes are usually accidental findings and are of no importance.

The menstrual periods are followed by the effusion of blood into a ruptured Graafian follicle. Normally, the amount of blood is small; it becomes solid, is decolorized, and then gradually is absorbed. Sometimes, the effusion of blood is much greater, so that the follicle filled with blood is as large as a pigeon's egg. The blood remains in the follicle and is absorbed, or, rather, replaced by fibrous connective tissue which wanders into the fibrin network of the clot from the periphery. More rarely, it is replaced by a serous fluid, and in exceptional instances, it may, through rupture, escape into the peritoneal cavity. Death has been known to ensue from the hemorrhage; sometimes the blood collects in Douglas's cul-de-sac and becomes encapsulated. Hemorrhages also occur in follicles which have become cystic. Interstitial hemorrhage in the ovary sometimes occurs without known cause.

[1] *Biland, J.*, Zieglers Beitr., 1907, xl, 195 (bibl.).

INFLAMMATION. (Oophoritis.)

Acute Exudative Inflammation of the ovaries occurs most frequently in the puerperal condition, either as part of a general peritonitis or as a primary affection, through direct extension by the lymphatics or, more rarely, metastatically through transportation of bacteria by the blood current.

In puerperal peritonitis, both ovaries are usually inflamed; they are swollen, congested, soft, infiltrated with serum or pus, and gangrenous. The lesion may involve principally the capsule, the stroma, or the follicles. Inflammation of the capsule results in adhesions and collections of pus, shut in by false membranes; inflammation of the stroma, in abscesses and fibrous induration; inflammation of the follicles, in their dilatation with purulent serum.

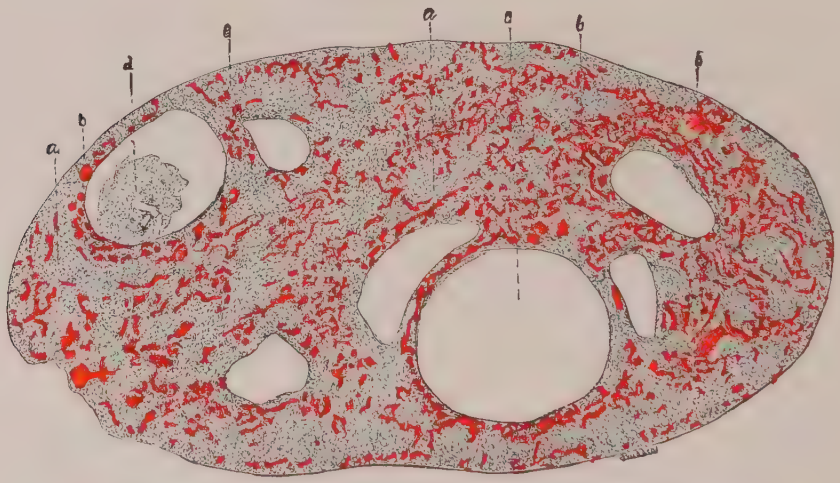


FIG. 644.—CHRONIC OOPHORITIS WITH DILATED BLOOD-VESSELS AND CYSTS.

1, Dense connective-tissue stroma; *b*, dilated veins; *c*, cysts; *d*, cyst with granular contents; *e*, cortical zone of immature Graafian follicles.

If the inflammation of the ovary be the primary lesion, and this must be considered the utmost rarity, it is usually confined to one organ. The stroma of the ovary is infiltrated with serum and pus, and may contain abscesses of large size. In other cases, the ovary itself is but little changed, but it is surrounded by a mass of fibrinous and purulent exudation. Such independent forms of ovarian inflammation may terminate in recovery; or the abscesses may perforate into the free peritoneal cavity, causing peritonitis, or into the rectum and vagina; or the ovary may be left indurated and bound down by adhesions.

Acute exudative inflammation of the ovaries unconnected with the puerperal condition is not common, but it may occur in connection with acute or chronic peritonitis or perimetritis, with various infectious diseases (mumps, diphtheria, typhus fever, pyemia, etc.).

Chronic Oophoritis, though described by many authors, must, per se, be a great rarity (Fig. 644). Usually the condition is the residuum from an acute puerperal or postabortive infection, or it is the final stage of a gonorrheal process. In the latter case, characteristic tubal changes will be found which show the mode of origin long after live gonococci have disappeared.

As the result of repeated attacks of salpingo-oophoritis, the organ may finally be smaller than normal, because of the formation of dense new interstitial connective tissue, and its surface may be greatly roughened and distorted. The atrophied ovary may be made up largely of thick-walled arteries and of fibrous masses which are the result of incomplete resolution of the corpora lutea (Fig. 645).

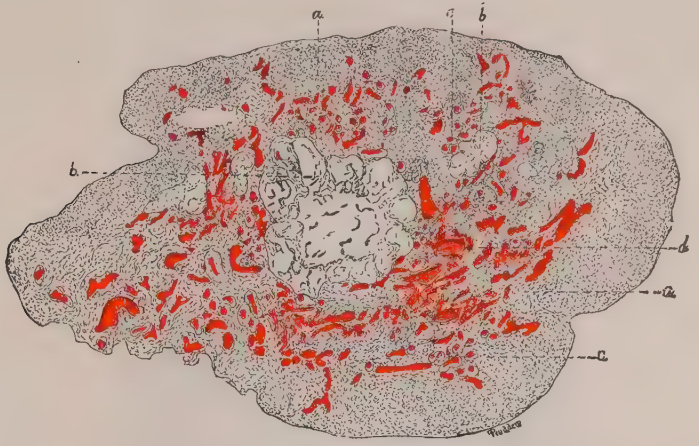


FIG. 645.—CHRONIC OOPHORITIS WITH ATROPHY.

From a case of valvular disease of the heart with chronic metritis and endometritis. *a*, Thickened and dense interstitial tissue; *b*, old corpora lutea; *c*, arteries with greatly thickened walls; *d*, dilated veins.

The so-called *microcystic* ovary is sometimes classified as chronically inflamed. This peculiar change, by which the ovary is converted into a honeycomb mass of thin-walled, closely contiguous, small cysts, is probably functional and not inflammatory. For some unknown reason, the follicles develop to a certain stage, usually attaining the size of a small pea, fail to rupture, but are not absorbed, as is usual. In consequence of successive crops, the ovary becomes honeycombed and moderately enlarged. Its albuginea grows thicker. This condition is noticed especially in sterile women; it may be permanent, but in some cases is of transitory duration. A somewhat similar appearance is almost invariably found accompanying, perhaps causing, fibroids of the uterus.

Tuberculous Inflammation of the ovaries is moderately rare, and may accompany tuberculous inflammation of other organs, particularly of the peritoneum or Fallopian tubes. It usually results in the production of dense caseous nodules of considerable size. Tuberculous infection of recently ruptured Graafian follicles may occur, probably through the blood-stream.

Syphilitic Inflammation, in the form of gummata, is uncommon.

Actinomycosis of the ovary is occasionally encountered, usually in connection with actinomycosis elsewhere in the body. The organisms are found in the pus.

TUMORS.

Classification of tumors of the ovaries is more difficult than that of tumors of any other part of the genital tract. The simplest method is to divide the tumors into two main classes: connective tissue and epithelial.

The ovary being only partly covered by peritoneum (at the hilus), tumors of this organ may be free or may be covered by the peritoneal layer, depending upon the direction of their development. The pedicle will always consist of the mesovarium, and, as growth progresses, may include also the ovarian, infundibulopelvic, and broad ligaments. Tumors which grow into the broad ligament and become *intraligamentous* have the Fallopian tube running over their surface.

Fig. 646.—Papilloma of Ovary.

Torsion of the pedicle occurs in a certain number of cases. The twist of the pedicle may produce complete shutting-off of the circulation, hemorrhage, necrosis, and rupture of the growth with the formation of adhesions or the development of peritonitis.

Connective Tissue Growths.

Fibroma is not common,[1] forming only about two per cent of all tumors occurring in the ovary, nor, when it occurs, is it usually of great importance. The tumors may be small or large; they are usually dense in texture, and seem often to originate in the tissue formed in the closure of the ruptured Graafian follicle. They may contain cysts or be accom-

[1] *Hellman, A. M.*, Surg., Gynec., and Obst., 1915, xx, 692 (bibl.).

panied by cysts of the surrounding stroma. Fibromata of the ovary usually produce massive ascites (in about 75 per cent. of the cases). *Papillary fibromata* of the surface of the ovary are not infrequent (Fig. 646). They may contain cysts (Fig. 647) and the growth may be transplanted from this situation to the general peritoneal surfaces. **Angioma** has been described.

Chondroma of the ovaries has been described, but is rare; cartilage occurs not infrequently, however, in dermoid cysts and in teratomata (Fig. 665, page 992).

Fig. 647.—Papilloma of Ovary.
Shows cyst with papillary growth within.

Osteoma is probably always secondary to ossification of a calcified focus,[1] except where the bone represents the overgrowth of one tissue in a dermoid cyst.

Leiomyoma, containing more or less fibrous tissue, is of occasional occurrence.

Sarcoma of the ovaries is not common, making up only about 5 per cent. of all ovarian tumors. It is usually primary, but may be metastatic. Fifty per cent. of the ovarian tumors occurring in children are sarcomata, small round-cell tumors predominating at this period. In adults, spindle-cell sarcomata are more often found. Polymorphous-cell tumors and even giant-cell sarcomata of the ovary have been reported

[1] *Moschcowitz, E.*, Proc. New York Path. Soc., 1913, xiii, 19.

(Fig. 648). Sarcomata of the ovary are very malignant, especially the softer forms; recurrence with metastatic involvement of the retroperitoneal lymph-nodes is almost the rule. The tumors may be hard or soft, and in about 10 per cent. of the cases involve both ovaries.[1]

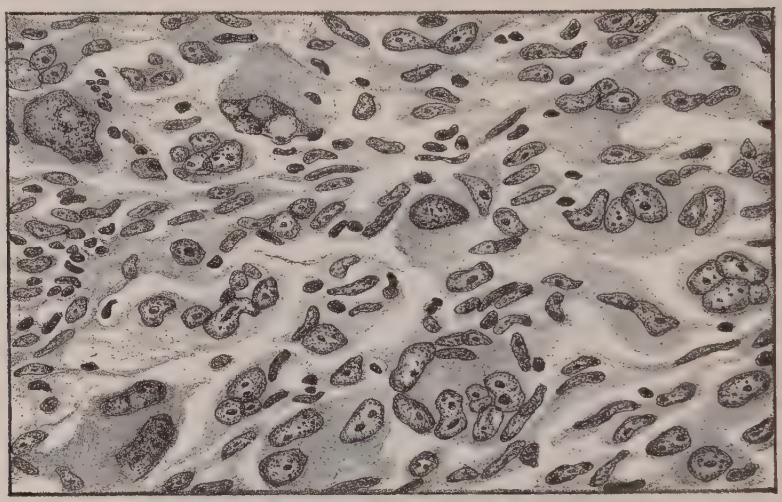


Fig. 648.—Sarcoma of Ovary.—Giant-cell Type.

Endotheliomata have been described in the ovaries, though tumors of this morphology are now more usually classed as carcinomata.

Fig. 649.—Follicular Cysts of Ovary.
At the right an old corpus luteum is visible.

Epithelial Growths.

Retention Cysts.—Follicular Cysts of the Ovary.—The Graafian follicles may be dilated so as to form cysts. The condition may occur in one

[1] *Smith* and *Motley*, Surg., Gynec., and Obst., 1915, xx, 419 (sarcoma of both ovaries in child of three years).

or both ovaries, and the cysts may be small or large, single or multiple (Fig. 649). They are usually found after middle life, but may occur during youth or childhood, or even in the fetus. The follicles dilate from the accumulation of fluid within them; the ovum is destroyed, and the epithelium flattened. The contents are usually serous and colorless, but may be viscid, purulent, or variously colored, red, yellow, or brown. The ovary may be crowded with numerous cysts of moderate size, whose adjacent walls may coalesce and atrophy, forming communications between them.[1] For the origin of "chocolate cysts" see p. 958.

Corpus Luteum Cysts.—A variety of this type of cyst is formed by the dilatation of a corpus luteum, either with or without the hyperplasia of the wall.

Lutein Cysts of Ovary.—Hydatid mole of the uterus in a large percentage of cases, and chorionepithelioma occasionally, cause multiple

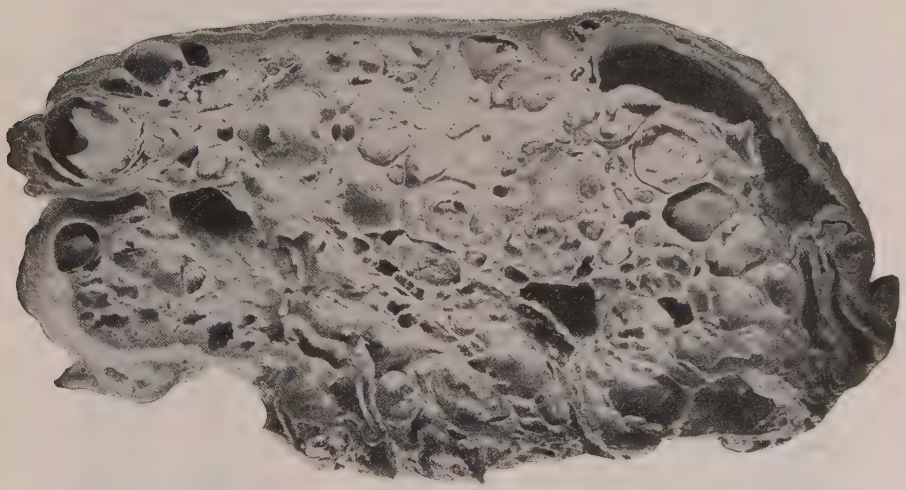


Fig. 650.—Cystadenoma of Ovary—(Multilocular Ovarian Cyst—Cystadenoma). About four-fifths natural size.

cystic dilatations of atresic follicles. The ovaries may attain the size of an adult fist. The cysts have thin walls and are often denuded of epithelium, but contain many lutein cells in the stroma. After expulsion or removal of the mole, the ovaries may resume a natural size, though this does not always occur.

Adenomatous Cysts.—Cystadenomata.—The best classification of these tumors is based upon the nature of the cyst contents, and is supplemented by the characteristics of the lining epithelium. The older classification of "glandular" and "papillary" types can not be maintained, because the so-called cystadenoma "glandulare" or "pseudomucinosum" may contain papillary outgrowths.

Cystadenoma pseudomucinosum contains a fluid varying from watery to jelly-like consistency, which is not precipitated by acetic acid.

[1] *v. Kahlden, C.*, Zieglers Beitr., 1900, xxvii, 1 (bibl.).

Cystadenoma serosum contains a fluid with high albumin content.

Cystadenoma (pseudomucinous, glandular, simple, or multiple).—There is a marked tendency in this form of adenoma to the formation of cysts. There may be a number of cavities equally dilated so as to form a number of cysts of moderate size (Fig. 650); or a few follicles may be greatly dilated to form a large *multilocular* cyst with but few compartments (Fig.

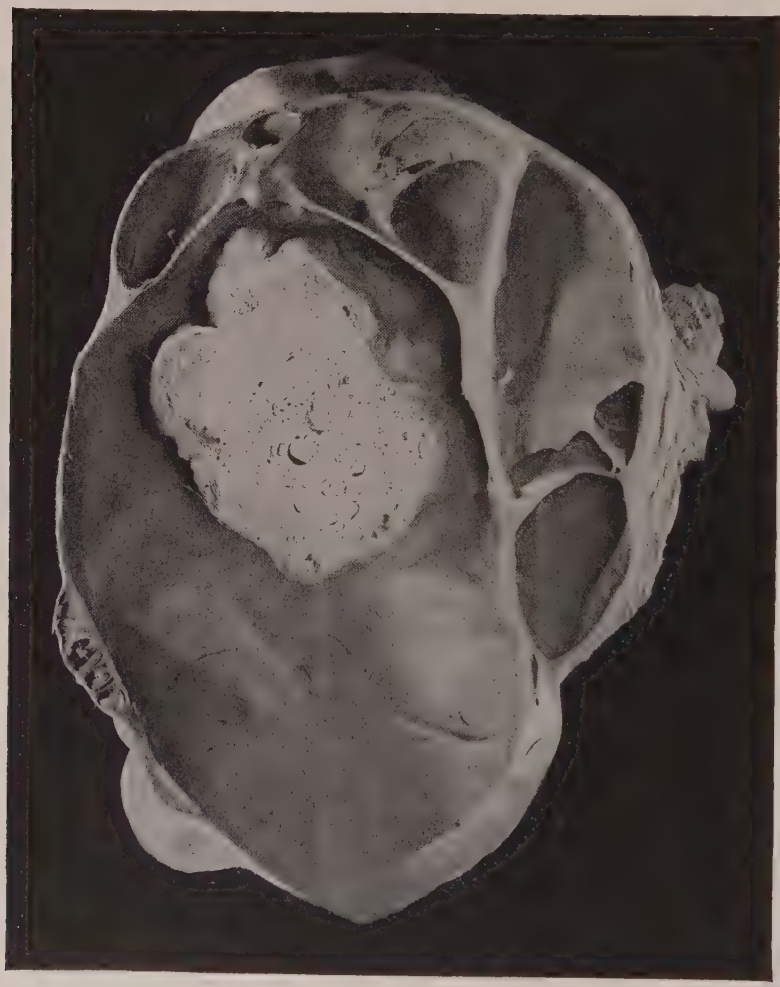


FIG. 651.—PSEUDOMUCINOUS CYSTADENOMA OF OVARY.
Showing large cysts, with a glandular mass within one of the cysts.

651). The walls of the cysts may fuse together and be absorbed, so as to form one large cyst divided by incomplete septa—*unilocular* cysts. The stroma in which the follicles and cysts are embedded may be largely developed or very scanty.

The walls of the larger cysts are composed of fibrous tissue which is

dense in the outer layers, more cellular in the inner, upon which the epithelium is placed. They may be thin and membranous, or there may be upon their internal surfaces an intracystic growth composed of a fibrous stroma and tubular follicles. These secondary follicles may also be filled with fluid and form larger and smaller cysts. The intracystic growths may be so large as to fill up the original cysts. Sometimes the

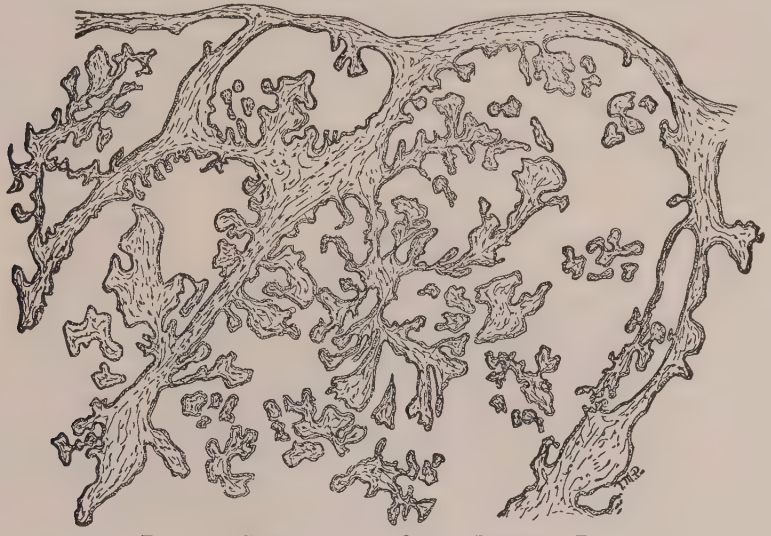


Fig. 652.—Cystadenoma of Ovary—Papillary Type.

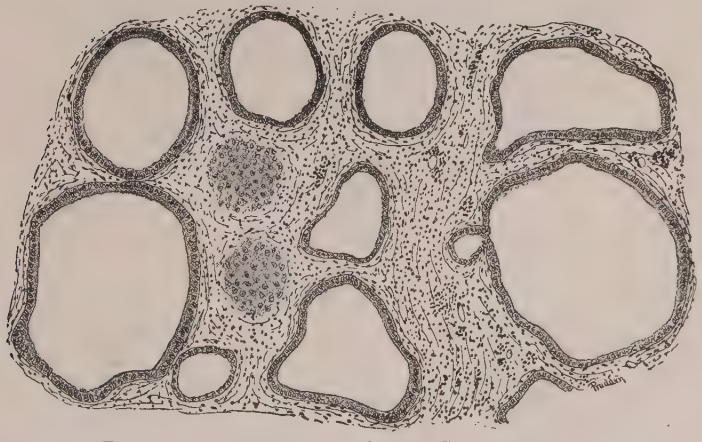


Fig. 653.—Cystadenoma of Ovary—Glandular Type.

intracystic growth presents very little dilatation of its follicles, so that the entire tumor has the character more of a solid growth than of a cyst. Flat papillæ are not infrequently found on the inner surface of the cyst walls. They rarely attain the height of the papillary growths commonly occurring in cystadenoma serosum (Fig. 652).

The cylindrical epithelium lining the cysts usually forms a single layer (Fig. 653), but several layers, often irregular in thickness, may form, and, owing to the accumulation of fluid, the cells may become flattened and atrophied, or they may be fatty or desquamated. The lining cells are usually columnar, with a clear protoplasm and with a deeply staining rod-like nucleus at the basal periphery. Goblet cells are noted between the more columnar structures, representing cells ready to discharge their secretion. The contents of the cysts differ considerably in different cases, and even in different cysts in the same case. They may be tough and ropy, or gelatinous, or serous; transparent and colorless, or yellow, reddish, or reddish-brown; or they may be turbid and colorless, or variously colored—red, brown, or chocolate—depending upon the amount of blood effusion that has taken place into the cyst fluid.

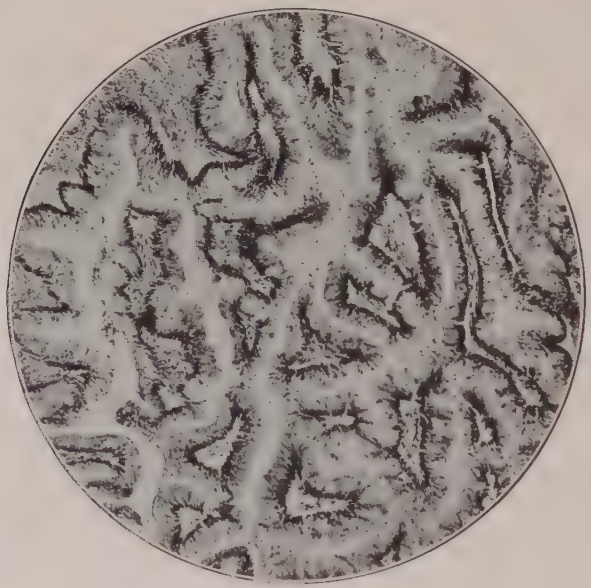


Fig. 654.—Pseudomyxoma of Peritoneum.

Chemically, the cyst contents include pseudomucin or paralbumin, and perhaps other less well-known compounds belonging to the same class. It is probable that the contents of these cysts are, so far as the pseudomucin and paralbumin are concerned, produced by a metamorphosis of the protoplasm of the lining cells, similar to that by which the mucin is produced in the mucous glands and in mucous membranes. Numerous degenerating cells from the cyst lining and white and red blood-corpuscles are found in the cyst fluid. In addition to the above structural elements, there may be found free fat droplets, cholesterin crystals, pigment granules, hematin, and more or less granular detritus. The gelatinous material filling these cysts is sometimes called *colloid*, and the cysts are frequently called *colloid cysts*.

Numerous secondary changes are likely to occur in these cysts. The cells may peel off, the walls of the cysts may atrophy or become calcified. Suppurative inflammation (infection with pyogenic bacteria, gonococcus, or typhoid or colon bacilli), perforation into the peritoneum, bladder, vagina, or rectum, hemorrhage, gangrene, etc., may occur. As a result of chronic productive processes, the cyst walls may become thickened and extensive adhesions may form. Carcinoma may develop from these tumors.

Cystadenoma pseudomucinosum is one of the most frequent of ovarian tumors (forming about 50 per cent.); it is of bilateral occurrence in less than 20 per cent., and is rarely malignant. Nevertheless, peritoneal implantations are noted, though these usually disappear after the cyst is removed. Occasionally, after spontaneous or traumatic rupture of a cyst, "*pseudomyxoma of the peritoneum*" develops (Fig. 654). This is a

FIG. 655.—MULTIPLE PAPILLARY CYSTS OF OMENTUM, SECONDARY TO A SIMILAR GROWTH IN THE OVARY.

The papillary outgrowths are themselves becoming softened at their centers, forming accessory cysts.

diffuse, sluggish growth, between the coils of intestine and other abdominal viscera, of a jelly-like material, containing columnar cells and pseudomucin (see page 808). Eventually, the abdomen distends to huge dimensions and death results from malnutrition or intestinal obstruction. Pseudomyxoma of the peritoneum may also result from the rupture of a pseudomyxoma of the appendix. Very rarely, during an operation, particles from ovarian cyst contents become implanted in the abdominal or vaginal scar and later lead to local recurrence at these sites.

Usually, ovarian cysts of this type produce symptoms merely because of their size, through the formation of adhesions, or because of torsion of their pedicle.

Cystadenoma Serosum (papillary).—This type of cystadenoma was formerly regarded as but a variety of the form described above—a variety characterized by papillary outgrowths in cauliflower-like tufts from the walls of the cysts, which often in large degree fill the cyst spaces.

The papillary cystadenomata are not, as a rule, so large as the glandular form. The cysts are usually fewer and contain, not colloid material,

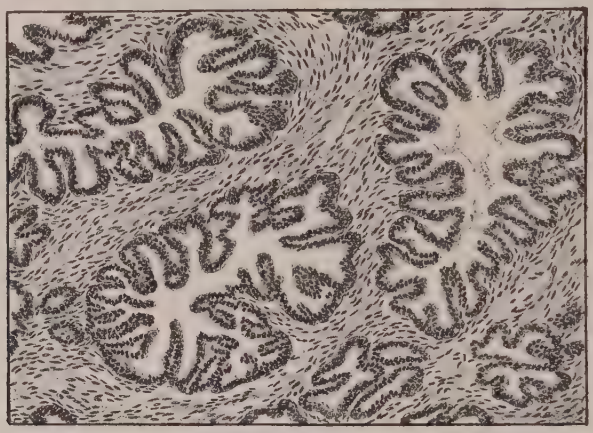


Fig. 656.—Papillary Cystadenoma of Ovary—Ciliated Cells.

Fig. 657.—Carcinoma of Ovary—Medullary Type.

but a thin watery fluid. One rare variety is composed of grape-like clusters of cysts attached to one another, in gross appearance much like a hydatid mole of the uterus. The papillary outgrowths often break

through the cyst walls, and may be transplanted to the peritoneal or other surfaces in the form of multiple cystic or papillary tumors (Fig. 655). The papillæ and cyst walls are lined with ciliated, cubical or columnar cells, containing a granular protoplasm and large nucleus (Fig. 656). The cells are, as a rule, in a single layer.

Malignant changes occur more frequently in serous than in pseudomucinous cystadenomata. The epithelium then becomes irregular, assumes multiple layers, and penetrates the stroma.

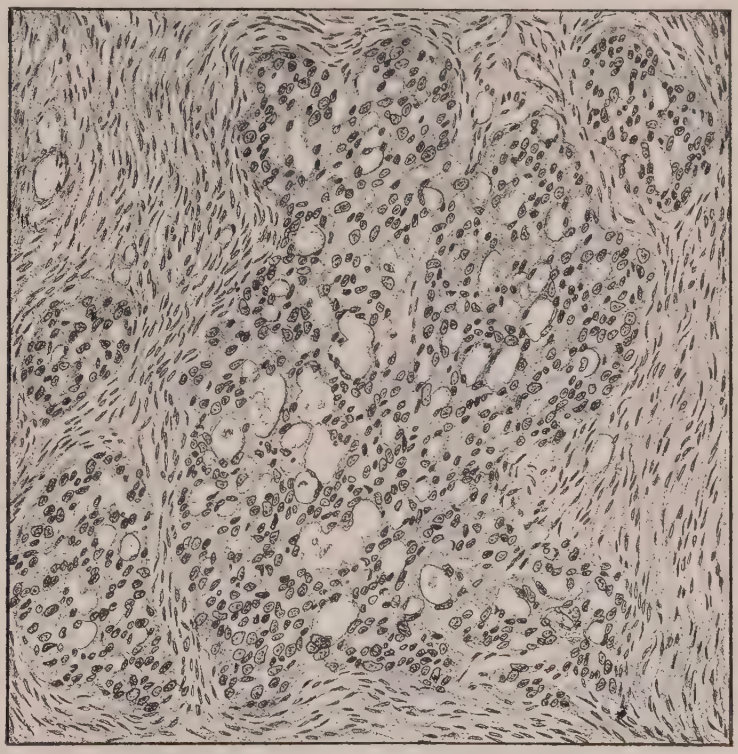


Fig. 658.—Alveolar Carcinoma of Ovary.

Clinically, serous cystadenoma is malignant. Recurrences appear in 75 per cent. of the cases; ascites is the rule; secondary peritoneal implantations are frequent and are less apt to disappear after removal of the ovarian tumor. On the other hand, in some instances even after incomplete removal of the growth permanent cure results.

Carcinoma, usually of the medullary variety, may occur as a primary tumor of the ovary (Fig. 657). It may be due to a continuous extension from neighboring organs or, more rarely, may be of metastatic origin. Although the medullary carcinomata are the most common, adenocarcinoma and scirrhous, melanotic, and gelatinous forms sometimes occur.

Macroscopically, carcinoma of the ovary may be either solid, partly

solid with cystic portions, or colloid. It may originate from carcinomatous changes in a cystadenoma or in a dermoid. In nearly 50 per cent. of the cases it is bilateral. The tumors may reach a large size, are friable when soft, and form adhesions early. They produce not only multiple peritoneal implantations, but also metastases in the lymphatics. After operative removal, recurrence is the rule (in about 90 per cent.).

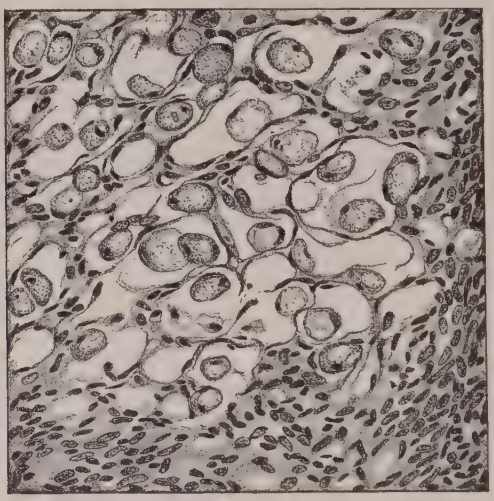


Fig. 659.—Krukenberg Tumor.
The primary growth was in the stomach.

Histologically, alveolar carcinoma is most common (Fig. 658). Pure adenocarcinoma is rarely found, alveolar distribution occasionally being apparent in small areas. Combinations of carcinoma and sarcoma (carcinosarcoma) are found most frequently in children. Such tumors probably are teratomata.

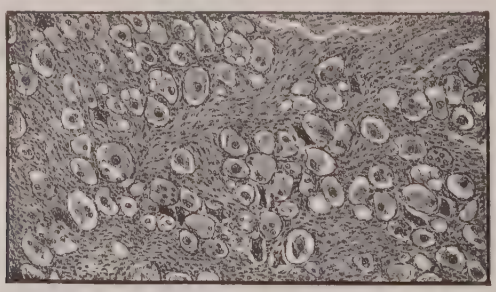


Fig. 660.—Ganglion Cells from Teratoma of Ovary.

Metastatic carcinoma, secondary to carcinoma of the intestinal tract, breast, and uterine fundus, occurs in the given order of frequency; the tumors are almost always bilateral. The cells of these tumors often produce a mucoid material which more or less fills the cell body and

pushes the nucleus to one side, giving a characteristic signet-ring appearance to the cells involved. The stroma may be unusually cellular so that the tumor is with difficulty distinguishable from a sarcoma (Fig. 659). It was for this reason called *fibrosarcoma ovarii mucocellulare* (*carcinomatodes*) by Krukenberg[1] who first described it, and by whose name also it is known. The secondary nature of this growth has been only recently determined.[2]

Teratomata (Dermoids and Solid Teratomata).

Both *dermoid cysts* and *teratomata* probably develop from embryonal cells which remain latent in the ovary for a variable number of years after birth. In dermoids, the tissues found resemble the adult type and show a tendency to form rudimentary organs. Representatives of all the embryonal layers (*ectoderm*—skin, hair, sweat and sebaceous glands,

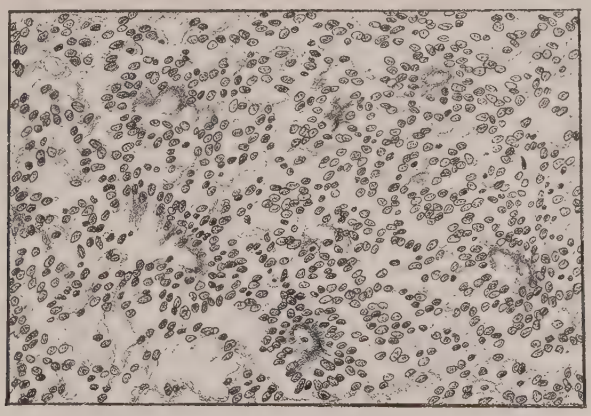


Fig. 661.—Glia Tissue from Teratoma of Ovary.

teeth, retina, nerve tissue (Fig. 660 and 661), etc.; *entoderm*—intestine, bronchi, etc.; and *mesoderm*—cartilage, bone, muscle) may be present, or only two or even a single layer may be represented (see also page 1043).

In teratomata, with few exceptions, the tissues are in the fetal stage of development, and elaborate organ formation is not seen. Teratomata likewise fail to develop large cysts with sebaceous contents, forming more solid tumors riddled with small cysts.

Dermoid Cysts (Embryomata).—These cysts may be uni- or multilocular, and are usually of moderate size, though they sometimes become as large as a man's head or larger. Multiple dermoids in one ovary are not uncommon, and bilateral occurrence is also not infrequent. The fibrous walls of the cysts may be thick or thin, and portions of the internal surface may present more or less completely developed cuticular struc-

[1] *Krukenberg*, Arch. f. Gynäk., 1895–96, l, 287.

[2] For discussion and bibl., see *Metzger, M.*, Les métastases ovariques des cancers digestifs, Paris, 1911; *Hall, M. E.*, Proc. New York Path. Soc., 1912, xii, 57; and *Stone, W. S.*, Surg., Gynec., and Obst., 1916, xxii, 407; *Major, R. H.*, Surg., Gynec., and Obst., 1918, xxvii, 195 (bibl.).

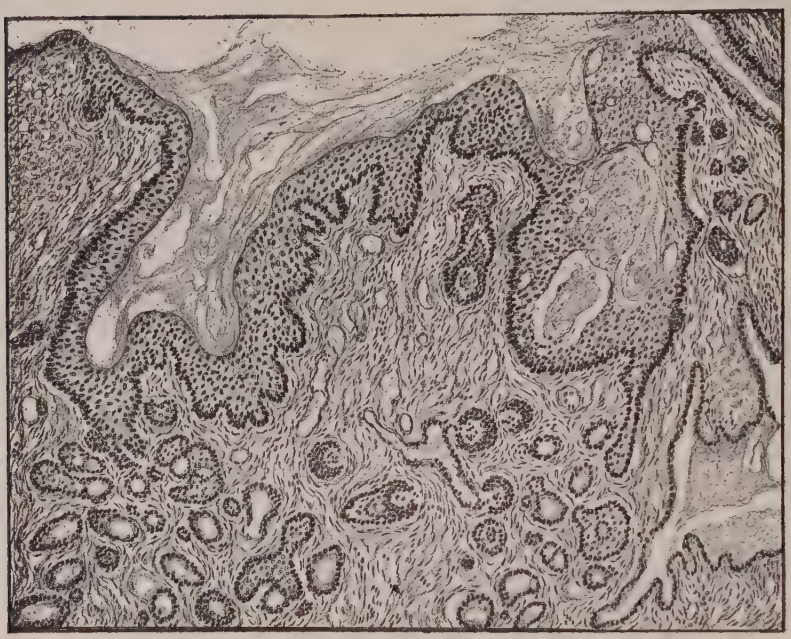


FIG. 662.—TERATOMA OF OVARY.
Showing skin and rudimentary hair follicles.

FIG. 663.—DERMOID CYST OF OVARY.
One of the cysts contains a mass of hair and sebaceous material.

tures, such as corium, papillæ, epidermis, hairs and hair follicles, sebaceous glands, etc. (Fig. 662). The cavity may contain a thick, whitish, greasy material composed of flattened epithelium, fat, or cholesterin crystals. Or the cavity or walls may contain masses of irregularly formed hair (Fig. 663), teeth, bone, cartilage, pharyngeal ciliated epithelium, striated muscle, thyroid gland (Fig. 664),[1] and nerve fibers and cells.[2]

Dermoids are divided into tumors containing all three embryonal layers, those containing two layers, and those rare tumors which contain

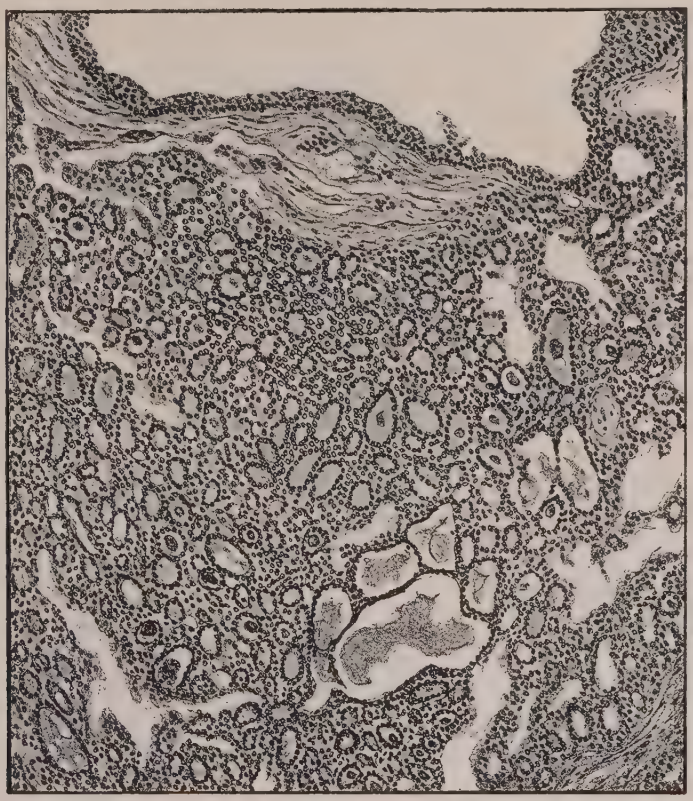


Fig. 664.—Thyroid Tissue in Dermoid of Ovary.

only one. It is possible to trace an unbroken series, from cases of so-called *fetus in fetu*, in which a more or less complete individual has been found in a dermoid cyst, through the less regular dermoids with only part of an individual, such as the upper jaw with full set of teeth and other organs only rudimentary in development, to a single layer dermoid, as, for example, the thyroid tumors of the ovary (*struma ovarii*), in which

[1] For a résumé with case of thyroid tissue in the ovary (struma ovarii), see *Frank, R. T.*, Am. Jour. Obst., 1909, lx, 433; see, also, *Fiebach*, Zieglers Beitr., 1911, li, 648.

[2] For a study of the origin of dermoid cysts of the ovary, see *Arnsperger*, Virchows Arch., 1899, clvi, 1; and *Askanazy*, Die Dermoidcysten des Eierstocks, Bibliotheca Medica, Abth. C., Heft 19, Stuttgart, 1905.

only thyroid tissue is found. Saxer reports having found a tooth embedded in an otherwise healthy ovary; R. Meyer has found the lens of the eye.

The commonest form of dermoid has a projection on the inner wall of the cyst, the so-called dermoid "papilla," which may be regarded as the embryonal anlage. From this region the hair arises, and on sectioning the papilla, the various structures above enumerated may be found.

A number of cases in which cancer has developed in the skin layer of the dermoid are recorded. The carcinoma is of the squamous-cell type (epithelioma). It may be accidentally found on sectioning the

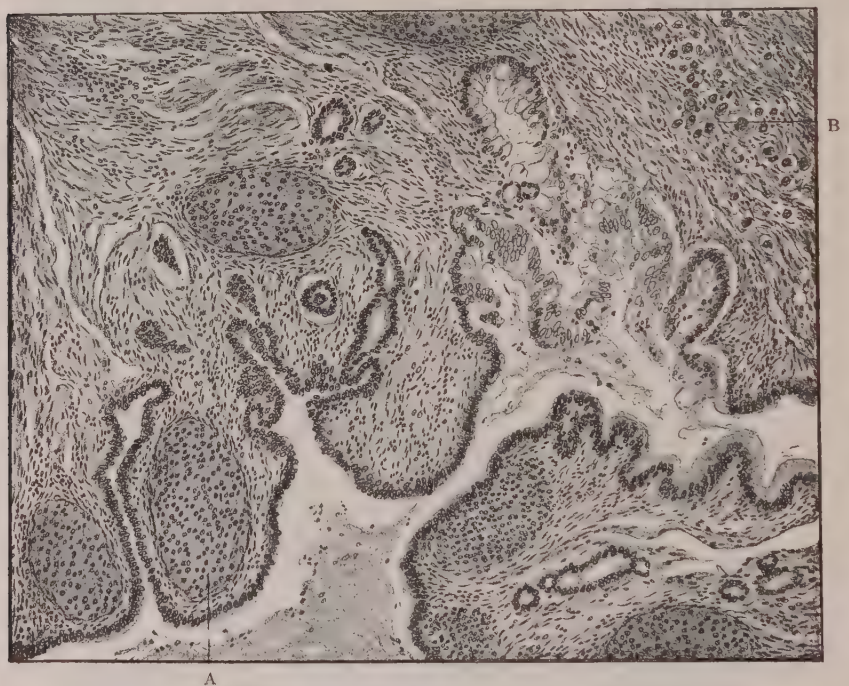


FIG. 665.—TERATOMA OF OVARY.
A, Cartilage. B, Ganglion Cells.

growth, or it may produce clinical symptoms by extending to neighboring organs or by causing metastases.

Such embryonal growths may exist for many years without causing inconvenience; but inflammatory changes may occur in them, leading to adhesions and perforations into adjacent organs. They may form the nidus for the development of carcinoma, chorionepithelioma (page 970), and other tumors, or they may calcify.

Teratomata,[1] as previously mentioned, are more irregularly developed, and are structurally of an earlier stage than dermoids. The tissues are of the early fetal period. Hence, myxomatous connective tissue, sar-

[1] *Wilms, M.*, Zieglers Beitr., 1896, xix, 367; *Sjövall, E.*, Frankfort. Ztschr. f. Path., 1911, vii, 10.

coma-like and carcinoma-like stretches are inextricably intermingled, riddled with cysts lined by varying epithelium. Cartilage, bone, undifferentiated striated muscle, neuroglia cells, etc. (Fig. 665), occur. These

FIG. 666.—SMALL PEDUNCULATED CYST GROWING FROM BROAD LIGAMENT.

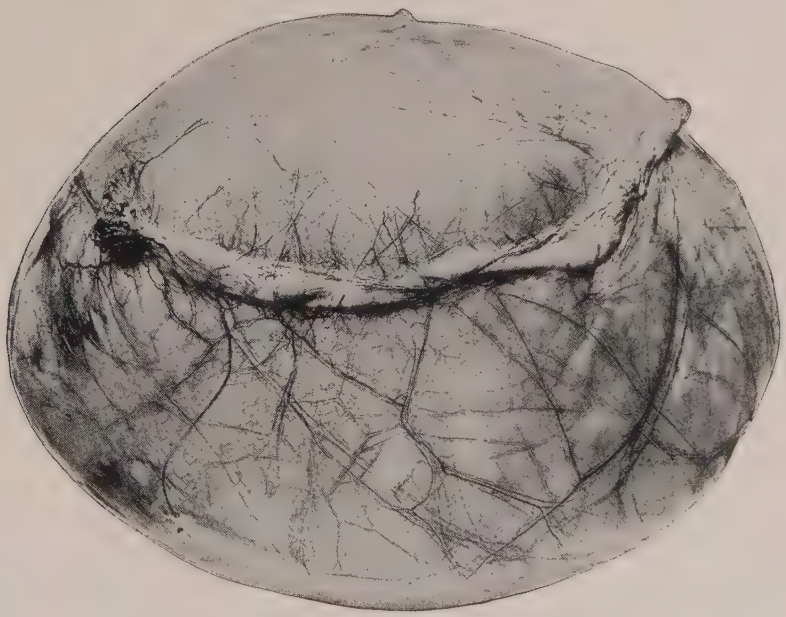


FIG. 667.—PAROVARIAN CYST OR INTRALIGAMENTOUS CYST.
The tumor measured about 10 cm. in its longest diameter.

solid tumors are usually malignant and may metastasize. The metastases are usually sarcomatous, but, at times, "organoid" metastases, similar to the primary growth, are encountered.

In addition to the above described dermoid cysts, there are a number of composite forms of not infrequent occurrence. Thus, in connection with dermoid cysts or separately, there may be simple ciliated cysts or combinations of both pseudomucinous and dermoid cysts. These may be multilocular and be lined with flattened, cylindrical, or ciliated epithelium, and may contain epidermal cells, cholesterin or mucin, etc.

Small cysts, sometimes pedunculated, sometimes not, of doubtful origin and usually of no special significance, are frequently found growing from the broad ligament near the ovary (Fig. 666). The walls are usually very thin, and lined with flattened epithelial cells, and the contents are serous.

Cysts of the Parovarium lie between the peritoneal layers of the broad ligament, and hence have a double vascular network on their surfaces (Fig. 667). They are usually small, but may be as large as a man's head They are lined usually with ciliated epithelium, but sometimes with non-ciliated cells. The contents may be serous, or may be thick and contain mucin and paralbumin.

The Fallopian Tubes.

Malformations.

Absence of both tubes occurs with absence of the uterus. One tube may be absent, with arrested development of the corresponding side of the uterus. Both tubes may be imperfectly developed; either of their ends may be closed; they may be inserted into the uterus at an abnormal place; they may terminate in two or three abdominal ostia. Diverticula in the tube are common. Accessory tubes have been found.

Changes in Size and Position.

The Fallopian tubes may participate in the various malpositions of the uterus and ovaries; but they are most frequently displaced by the contraction of adhesions formed in perimetric and periovarial inflammations.

The lumen of the tube may be partially or completely closed as the result of inflammation of the mucous membrane; of peritonitis about the fimbriated extremity; of tumors or inflammation of the uterus; or by pressure from without, or by adhesions, tumors, etc. It may become stopped by plugs of mucus or pus. In inflammatory processes, the tube is closed either by false membranes which obliterate the opening without greatly affecting the fimbriæ, or, more commonly, by retraction of the fimbriæ (which are merely prolongations of the tubal mucosal folds over the peritoneal ring at the ostium). When inflammation occurs the fimbriæ are drawn inward as the tubal lumen distends through swelling or accumulation of fluid. The retracted fimbriæ are then agglutinated.

Dilatation of the tubes may be produced by an accumulation of catarrhal or other exudation, when there is partial or complete stenosis at some portion of the tube. The dilatation may be moderate, converting the tube into a tortuous, sacculated canal containing mucous or serous fluid; or, more rarely, large cysts may form containing several pounds of serous fluid—*hydrosalpinx*[1] (Fig. 668). In the mild grades of infection which produce hydrosalpinx, the tubal wall does not hypertrophy, but may become as thin as paper and translucent. It must not be forgotten that sometimes the final outcome of a pyosalpinx is a hydrosalpinx. Then, however, the sac wall usually is thicker.

[1] For a study of hydrosalpinx with full bibliography, see *Cullen, T. S.*, Bull. Johns Hopkins Hosp., 1895, v, 351.

Tubo-ovarian cysts are formed by coalescence of a hydrosalpinx and a follicular ovarian cyst or an ovary which has become cystic from inflammatory adhesions. Large complex masses are thus formed.

As the fluid collects, the epithelium may become flattened or fatty, or may desquamate. Inflammation may occur in the walls of the dilated tube, and the contents may be mixed with pus or blood. Rupture of the dilated tube sometimes takes place; or there may be severe and even fatal hemorrhage into its cavity. Papillary growths are sometimes found springing from the inner wall of the cyst.

Salpingitis Nodosa.[1]—The inflammation may be localized in the isthmic or interstitial part of the tube. The lesions appear as firm nodules, usually multiple, reaching the size of a pea or cherry, in the wall of the tube. On section, a labyrinth of small lumina, lined with normal tubal mucosa is found. The lumina all communicate with the main tubal cavity, as is shown by serial sections. With few exceptions, this disease is due to chronic inflammation. A small minority of cases may be due to adenomyomata of mesonephric origin (v. Recklinghausen).

FIG. 668.—HYDROSALPINX.
The tube at the left is much distended, but still tubular. The tube at the right is dilated to cystic form. Between the distended tubes is the fundus of the uterus.

HEMORRHAGE.

Hemorrhage[2] into the tube may occur in hematometra and tubal pregnancy, in acute infectious diseases, and in diseased tubes during menstruation. The blood may undergo degenerative changes and be largely absorbed, or it may escape into the peritoneal cavity and incite peritonitis.

INFLAMMATION. (Salpingitis.)

Inflammation of the mucous membrane of the Fallopian tubes commonly occurs in connection with endometritis, most frequently in an

[1] *Wallart, J.*, Ztschr. f. Geburtsh. u. Gynäk., 1910, lxvi, 130; 1913, lxxiii, 1.
[2] *Bazy, L.*, Rev. de gynéc., 1910, xv, 1.

ascending gonorrhea, which usually, though not invariably, progresses by a surface growth of the gonococci extending upward from the endometrium. In the puerperal infections, which, as a rule, are strepto- or staphylococcic in origin, the organisms more commonly propagate along the lymph-channels and, therefore, reach the tubal wall before they infect the mucosa. In the *acute* stage, the mucous membrane is hyperemic and swollen, and is covered with a mucous or mucopurulent, often bloody, exudate. Pus exudes from the tubal ostium and infects the neighboring peritoneum. In gonorrheal processes, the resulting peritonitis tends to remain localized, causing repeated attacks of pelvic peritonitis and adhesions; in strepto- or staphylococcic infections a more diffuse peritonitis, often with fatal outcome, is more common. During the acute stage, the tubal lumen contains fluid, leucocytes, plasma cells, and microorganisms. The mucous membrane is overvascular and infiltrated with plasma cells and leucocytes. Superficial erosions of the epithelial layer and coalescence with opposite folds are frequent.

The inflammation may subside, leaving no lesions, but it more frequently becomes *chronic*, and may then result in peritoneal adhesions, thickening of the walls, obliteration of the tubes, dilatations, etc.; or the mucous membrane may undergo hyperplasia with papillary outgrowth. Such papillary masses may partially coalesce, forming, on the accumulation of fluid, cyst-like cavities lined with epithelium. Hyperplasia of the muscle wall of the tube may be associated with these conditions.[1]

Suppurative Salpingitis.—Catarrhal inflammation of the mucous membrane may assume a suppurative character, sometimes in connection with puerperal metritis and peritonitis, and often as a result of gonorrheal infection.[2] Under these conditions the wall of the tube is involved. It is difficult in many cases of suppurative salpingitis associated with peritonitis, unless the clinical history makes the origin clear, to say which is the primary lesion.

If the abdominal end of the tube be closed[3] by adhesions or otherwise, there may be a considerable collection of pus in the tubes, causing dilatation—*pyosalpinx* (Fig. 669 and 670). Such a collection may rupture into the peritoneal cavity, or the pus may escape into a cavity shut in by adhesions, or may perforate into the intestine or bladder; or it may absorb and finally become calcified. In pyosalpinx, the tubal wall may be greatly thickened. In the acute stage, this is primarily due to exudation and invasion of leucocytes. Not only the tube, but its mesosalpinx also, then presents an edematous, tense, and glistening appearance. Later, when the condition has become more chronic, the tubal wall becomes fibrous, hard, and sometimes almost cartilaginous in consistence. In nearly two-thirds of all the chronic cases, the pus proves to be sterile on culture. Pus tubes may reach enormous dimensions, and usually sink down into the pelvic cavity and form dense adhesions with all neighboring viscera.

[1] *Ries, E.*, Jour. Exper. Med., 1897, ii, 347 (bibl.).

[2] For a study of gonorrheal salpingitis, see *Gurd, F. B.*, Jour. Med. Research, 1910, N. S. xviii, 151: *Miller, J. W.*, Monatschr. f. Geburtsh. u. Gyn.k., 1912, xxxvi, 211: and *Schridde, H.*, Die Eitrige Entzundüngen des Eileiters, Jena, 1910.

[3] *Opitz, E.*, Ztschr. f. Geburtsh. u. Gynäk., 1904, lii, 485.

The walls of a chronic pyosalpinx show an increase of fibrous tissue, an infiltrated thickened mucosa containing plasma cells, thickened tubal

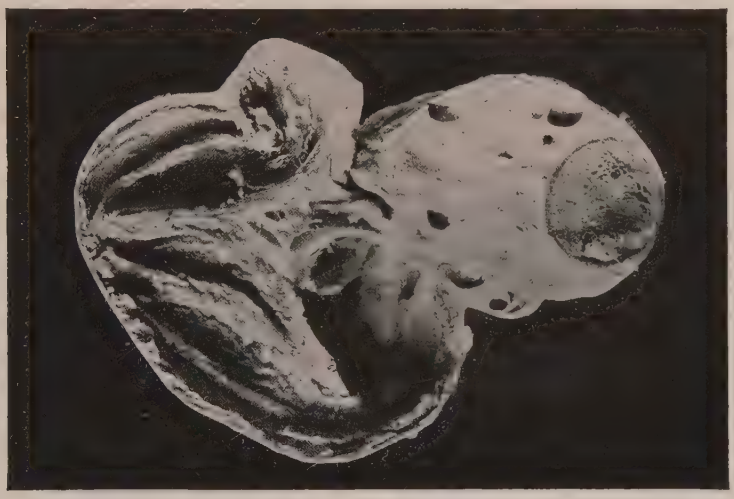


FIG. 669.—PYOSALPINX.
The distended tube containing pus is attached to the ovary.

folds, and, often, adhesions between adjacent rugæ. At times, innumerable coalescences of folds on cross-section give the appearance of many

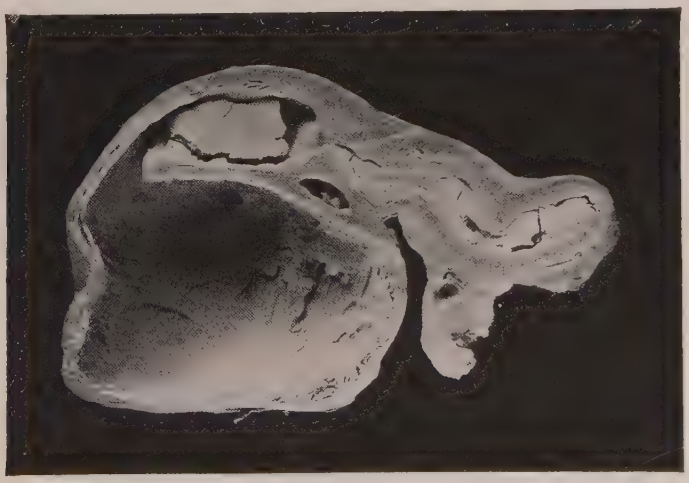


FIG. 670.—PYOSALPINX.
Showing a cyst-like distention of the occluded tube.

small cystic cavities. Although plasma cells are more commonly found in pyosalpinges of gonorrheal origin, their presence is not so absolute a criterion as was asserted by Schridde.[1]

[1] *Schridde, H.*, Die eitrigen Entzündungen des Eileiters, Jena, 1910.

Tuberculous Salpingitis.[1]—The lesions are most frequently seen in the later stages of the process, when the mucous membrane is partially or entirely converted into a thick caseous, often ulcerating layer (Fig. 671). The lumen of the tube may be dilated, and the wall thickened from chronic inflammation. This lesion may occur by itself, or may be associated with tuberculous inflammation of the lungs, of the other genitourinary organs, or of the peritoneum. It usually commences at the abdominal ends of the tubes, and both tubes are apt to be involved.

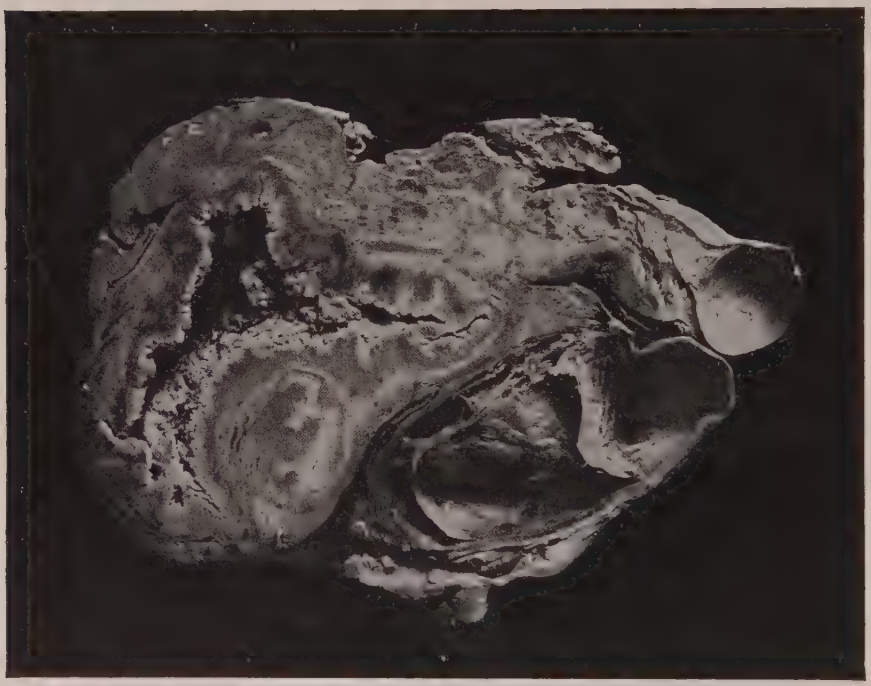


FIG. 671.—TUBERCULOUS SALPINGITIS.
The wall of a portion of the tube is converted into a dense mass of fibrous and necrotic tissue which is disintegrating.

At times, the peritoneal surface of an otherwise normal appearing tube is covered with miliary tubercles. This is usually due to widespread infection of the peritoneal serosa. The writer has seen three cases of hemorrhage from an apparently normal tube—hemorrhages into the free peritoneal cavity sufficient to produce symptoms of ruptured ectopic pregnancy—due to tuberculosis of the tubal mucous membrane. In the earlier stage of tuberculosis the mucosa shows large accumulations of epithelioid cells which greatly thicken the rugæ (Fig. 672). As the process advances, many tubercles, with giant cells, form, coalesce, caseate, and invade and destroy the musculature. The entire mucosa may be destroyed, a large sac lined with tuberculous granulation tissue resulting.

[1] *Simmonds, M.*, Arch. f. Gynäk., 1909, lxxxviii, 29; *Jung, P.*, ibid., 1910, xcii, 764; and *Engelhorn, E.*, ibid., 775.

Calcification may take place and most of the cases of so-called teratomata with bone formation which have been reported, have proved to be end processes of tuberculosis.

Syphilitic Inflammation, manifested by a gummatous thickening of the wall, has been described.

Actinomycosis of the tube, usually in connection with actinomycosis of the other pelvic organs, leading to abscesses and fistulæ, has been described.

PARASITES.

Echinococcus may occur in the tube. **Oxyuris,** also, has been found, the ova as well as the worms.

Fig. 672.—Tuberculous Salpingitis.

TUMORS.

Small **fibromata** and **fibromyomata** sometimes occur in the wall of the tubes or in the fimbriæ. Small **lipomata** and bits of adrenal tissue have been seen between the folds of the broad ligament in close connection with the tubes. **Papillomata** of a benign nature probably do not occur. **Myxoma** is recorded **Sarcoma** is rare.

Carcinoma of the tubes may be primary or secondary. *Primary* carcinoma,[1] which is the most common tumor of the tube, begins as a papillomatous outgrowth, spreading in the tubal lumen. The tube is usually retort-shaped, its ostium closed. The growth may break through the tubal wall, extending to the peritoneum, or may, by metastasis, involve the uterus, ovary, or regional lymph-nodes.

Histologically, a connective-tissue framework covered with a single,

[1] *Doran, A.*, Jour. Obst. and Gynec., Brit. Emp., 1904, vi, 285; 1910, xvii, 1; *Orthmann, E. G.*, Ztschr. f. Geburtsh. u. Gynäk., 1906, lviii, 376.

or more often, multiple layers of epithelium is encountered. The cells are of varying size and show irregular nuclei. In other areas, adenomatous configurations are assumed; in still other portions, solid cell masses invade the musculature.

Secondary carcinoma of the tube originates from carcinoma of the uterus, ovary, or gastrointestinal tract (colloid cancer).

Chorionepithelioma of the tube occurs, originating from an ectopic tubal pregnancy. The growth in its histological features is similar to chorionepithelioma elsewhere.

Cysts, usually of small size, sometimes pedunculated and with thin walls, are frequently seen in the peritoneal covering of the tubes or in the fimbriæ. They are believed to be of embryonal origin. Small collections of clear cells are occasionally found on the tubal surface. They may be adrenal in origin, but more frequently are derived from hyperplasia of the peritoneal mesothelium (Fig. 673).

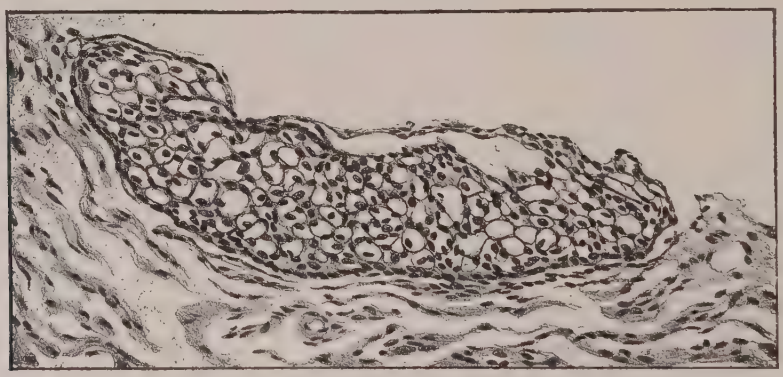


Fig. 673.—Small Cellular Masses of Mesothelial Origin on Peritoneal Surface of Fallopian Tube.

Extrauterine Pregnancy.

Tubal Pregnancy.[1]—The impregnated ovum, in some way hindered from passing into the uterus, may become fixed in the tube, and there develop (Fig. 674). The arrest of the ovum may be due to injury of the ciliated tubal epithelium from preceding inflammatory disease, to arrest in preformed diverticula,[2] to distortion of the tube by external adhesions, tumors, etc. A few instances probably due to *internal migration* (*i.e.*, cases in which the ovum from the left ovary, for example, wanders through the right tube) have been reported. The extra time consumed permits the ovum to acquire the erosive properties which, under normal circumstances, it attains only after it has reached the uterus. The villi of the chorion grow into the mucous membrane of the tube, forming an incomplete placenta.

[1] For a very full discussion of the older literature on the subject of ectopic pregnancy, see *Werth, R.* Winckel, Handbuch d. Geburtshilfe, Wiesbaden, 1904, ii, Part 2, p. 1.

[2] *Huffman, O. V.*, Surg., Gynec., and Obst., 1913, xvi, 548.

The placenta is incomplete because the tubal mucosa has neither the glandular elements nor the thickness of the uterine mucous membrane. Decidual reaction in the tube, when it does occur (and decidua can be detected in only a small number of cases) is incomplete. As the decidua is one of the strongest barriers against the invasion of the fetal elements, erosion of the musculature of the tubal wall is the common sequel of tubal nidation. For a similar reason, the fetal trophoblastic elements invade the maternal blood-vessels more freely than in intrauterine implantation (Fig. 675).

The tubal pregnancy may develop in the *interstitial*, *isthmic*, or *ampullary* portion of the tube. As the ovum and its chorion enlarge, the

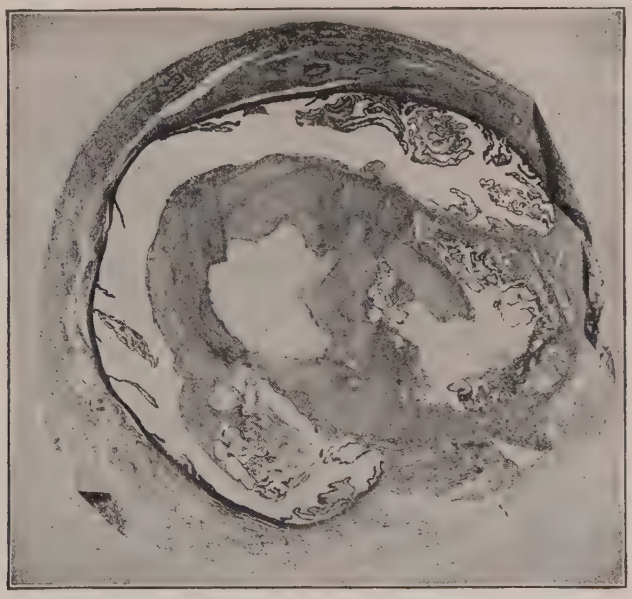


Fig. 674.—Cross-section of Unruptured Ectopic Pregnancy.
Masses of chorionic villi can be seen in the clot in the center of the tube

affected portion of the tube distends and forms a tumor of variable size.

From lack of nutrition, the ovum may die at an early stage, and may form a *blood mole*. This is a rare outcome.

More commonly, due to abundant erosion of blood-vessels, hemorrhage into the tubal lumen takes place. The partly clotted blood flows or is expelled through the peritoneal ostium and collects around the tube. If the ovum also is expelled the condition is called a *tubal abortion*. If the bleeding continues, a *hematocele*, usually situated in Douglas's cul-de-sac, arises. The peritoneal irritation causes the formation of adhesions and shuts off the blood in a closed cavity, its walls formed by fibrin which may organize and produce a firm structure. The blood-clot may become infected, producing a secondary abscess.

In about one-fourth of all cases, erosion of the tubal wall produces

tubal rupture. The large, torn blood-vessels of the placental site occasion severe intraperitoneal hemorrhage, which may prove rapidly fatal, or repeated smaller hemorrhages may lead to the same outcome. Interstitial pregnancies are especially prone to rupture. If the rupture takes place into the mesosalpinx an intraligamentary accumulation of blood results.

Both tubal abortion and tubal rupture are most frequent between the fifth and seventh weeks of gestation.

Exceptionally, the tube is not eroded and the placental circulation proves sufficient for the fetus. Under these circumstances, gestation continues to term within a dilated but unruptured tube. More commonly, though still very rarely, the ovum is gradually extruded, either

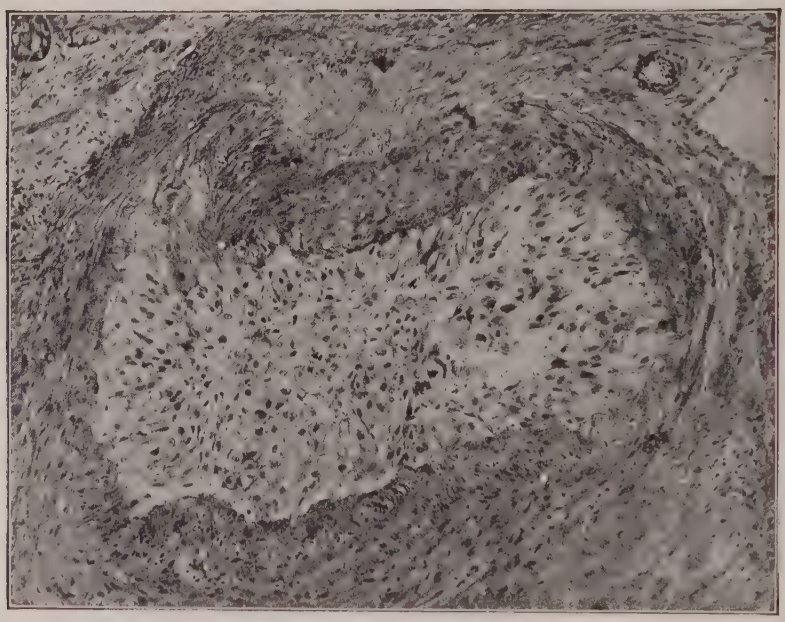


Fig. 675.—Ectopic Pregnancy.
Trophoblastic elements in vessel in wall of tube.

through the abdominal ostium or through a hole in the tubal wall, so slowly that it has the opportunity to form connections with neighboring organs. A *secondary abdominal pregnancy*, which may reach term, then ensues. The fetal membranes and placenta are agglutinated with the intestine, pelvic wall, uterine fundus, etc. When term is reached, the fetus dies, the amniotic fluid is absorbed, and the fetus may mummify and be impregnated with lime salts. This is termed a *lithopedion*. Such remains have been retained for long periods of years. At times they become infected and ulcerate through, and may be expelled per vaginam or rectum.

In tuboabdominal pregnancy the development of the ovum is in the

fimbriated extremity of the Fallopian tube. Adhesions are formed, so that the fetus is partly in the end of the tube and partly in the abdomen.

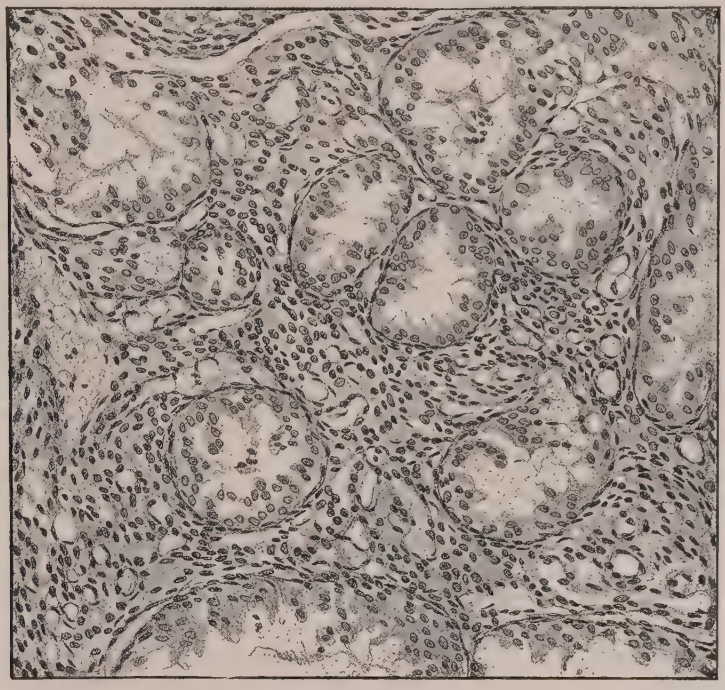


Fig. 676.—Endometrium in Ectopic Pregnancy.

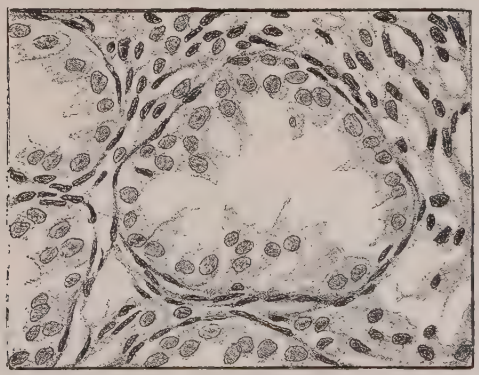


Fig. 677.—Endometrium in Ectopic Pregnancy.
(High power.)

Primary Abdominal Pregnancy.—The ovum, after escaping from the ovary, may not enter the Fallopian tube, but may become fixed to the peritoneum, usually near the ovary, and develop in that position.

Ovarian Pregnancy.—The existence of this form of pregnancy is no longer doubtful. There are some cases in which the ovum develops in its Graafian follicle. In others, it develops extrafollicularly.

Simultaneous intra- and extrauterine pregnancies have been reported.

TWIN TUBAL PREGNANCIES, either of the same or of both tubes, are on record.

Hydatid mole and chorionepithelioma developing from tubal gestation are known.

The *decidual reaction* produced by tubal pregnancy is of interest. Quite regularly, though not invariably, a massive decidual change takes place in the uterine mucous membrane beginning about the second month of gestation (Fig. 676 and 677). The change may include the cervix. The accompanying hyperemia produces the irregular bleeding and "spotting" usually seen in ectopic pregnancy. Not infrequently, the "*uterine cast*" is expelled per vaginam, and is a fleshy, triangular sac, resembling that seen in dysmenorrhea membranes, formed by the superficial layers of the mucosa, and showing glandular changes of pregnancy and well-marked decidual reaction of the stroma. Islets of decidual cells may also be found in the ovary, peritoneum, appendix, etc., even more frequently than in intrauterine gestation.

The Mamma.

Embryology and Anatomy.

At about the second month in the mammalian embryo there is a thickening of the ectoderm extending as a ridge on either side from the axillæ to the groins. Soon this line, which is the anlage of the future mammary glands, is broken up into wart-like buds. Between the fourth and fifth months, the epidermis grows down into the connective tissue of the mammary area; these solid processes send off a number of sprouts which form the milk ducts and, finally by further growth and branching, the glandular tissue of the mamma.

The acini are lined with a layer of cylindrical and an outer layer of cubical or flattened epithelium, and possess a membrana propria of connective tissue. The ducts have a flattened cell lining and a wall of connective and elastic tissue. The presence of muscle fibers in the walls of the ducts and acini is both affirmed[1] and denied.

The lacteal structures in the adult form only a small portion of the mamma in the resting phase, but during lactation there is a great increase in the size and number of the glands. The milk fat is brought to the breast in soluble form, and is secreted by the glandular epithelium in the form of granules which occupy all of the cell except the nucleus. The granules are extruded into the lumen of the alveolus, after which the cell regenerates.[2] After lactation is completed, these glands largely regress. In the breast in which lactation is beginning or which is the seat of chronic cystic mastitis, the acini contain colostrum corpuscles, which are large cells filled with fat granules. They are either desquamated epithelium from the walls or phagocytic cells which have wandered into the ducts from without[3] and collected the fat. The interstitial tissue is composed of coarse collagen fibers and but few nuclei. Fat tissue forms most of the bulk of the remaining structures of the lactating mamma. Numerous sweat and sebaceous glands are present about the nipple.

At the menopause, there commences the process of senile involution, in which there is a gradual disappearance of the glandular structure, often with an increase of the adipose tissue in the breast.[4]

[1] *Kuru, H.*, Deutsch. Ztschr. f. Chir., 1909, xcviii, 415.
[2] *Arnold, J.*, Zieglers Beitr., 1905, xxxviii, 421.
[3] *Thomas, E.*, Ztschr. f. Kinderheilk., 1913, viii, 291.
[4] For normal histology, see *Berka*, Frankfurt. Ztschr. f. Path., 1911, viii, 203.

The mammary gland is inclosed in a capsule formed by two layers of fascia. It receives its blood supply from branches of the axillary, internal mammary, and intercostal arteries. The lymph-nodes receiving vessels directly from the breast are the axillary, retrosternal, retropectoral, supraclavicular, deep cervical, and paramammary. The axillary groups are most often invaded by carcinoma from the breast, the retrosternal chiefly in tumors of the inner quadrant; the retropectoral nodes are few in number and are not often invaded; the deep cervical are invaded in only a small percentage of carcinomata. The adjacent lymph-nodes which may become involved late in carcinoma of the breast are the axillary of the opposite side, diaphragmatic, hepatic, supraxiphoid, upper brachial, intercostal, and inguinal.

Physiology and Pathology of Function.

The first sign of any activity in the mammary gland is frequently shown in both sexes within a few days after birth; at this time a few drops of a milk-like substance can often be expressed from the nipples, and this is frequently accompanied by a slight swelling and tenderness of the breasts. This "*witch-milk*" is composed largely of desquamated cells and degenerated products, and is not a true lacteal secretion.[1] From this time until puberty, the mammary glands are quiescent except in those occasional cases in very young girls where the breasts enlarge until they attain their full size and are even seen to functionate. Such conditions of *infantile hypertrophy*, however, are uncommon

From puberty until the menopause, the glands functionate with the advent of each pregnancy, whether it proceed to term or not. There is often a slight premenstrual hyperemic increase in the size of the breasts, and rarely the appearance of small quantities of blood at the nipple (*vicarious menstruation*). At the termination of each pregnancy or lactation, the glands return to their normal non-functionating state.

Arrest of develpoment of the mammæ may occur alone or, more frequently, as a sequela to arrest of development of the other reproductive organs. This has repeatedly been shown when the ovaries have been removed before puberty. Failure of proper function of the thyroid or pituitary gland is often accompanied by imperfect sexual or mammary development. Excessive or perverted function of the pituitary or adrenal gland may cause premature enlargement of the breasts.

Enlargement of the breasts and the secretion of milk has been observed to coincide with the occurrence of tumors of the ovary, especially of the malignant type. Conversely, the removal of the ovaries may check for a few months or a year the growth of a carcinoma of the breast or the development of metastases.

Malformations.

Absence of one or both mammary glands is known as *amastia* and is noted in both sexes; together with undeveloped mammary glands, *micromastia*, it is an nucommon condition due to some developmental detect. Absence of one or both nipples, *athelia*, is a rare condition also. Supernumerary mammary glands, *polymastia*, at one time considered comparatively rare, are now known to be frequent; and the literature abounds with references to their occurrence in both sexes and on almost every portion of the body.[2] In many cases these supernumerary glands are inactive, but in females they may become functionally active at each pregnancy and differ in no way from the normally situated glands; in the male also these glands may secrete milk. Adenoma or carcinoma may develop in them. In the axilla the sweat and sebaceous glands may undergo hyperplasia during pregnancy and may closely simulate mammary tissue.[3] The same condition may appear with acute infections of the axillary skin glands. When the glands assume an excessive size in the male, the condition is known as *gynecomastia*.

Occasionally an extra nipple is found on a normal breast or elsewhere; this condition is known as *polythelia* and is of great rarity, for supernumerary nipples are usually associated with polymastia.

[1] *Raubitschek, H.*, Ztschr. f. Heilk, 1904, N. S. v, 16.
[2] *Kayser, F.*, Arch. f. Gynäk., 1908, lxxxv, 459.
[3] *Seitz, L.*, Arch. f. Gynäk., 1906, lxxx, 517; 1909, lxxxviii, 94.

HYPERTROPHY.

A few cases are reported in which hypertrophy of the breasts was present at birth. Hypertrophy of the adult mammary gland is not very rare, and is due to enlargement of the mammary tissue itself (Fig. 678). In some cases the breasts are of enormous size, and of very rapid growth. The condition is more often found in both breasts, though it has appeared as a unilateral hypertrophy in many instances. The hypertrophy may begin at puberty, but usually the change occurs during pregnancy or may follow it. Occasionally the hypertrophy disappears spontaneously. Nothing so far is known as to the cause of the condition.[1]

FIG. 678.—HYPERTROPHY OF THE MAMMA.

Histologically the glandular parenchyma is increased as well as the stroma between the glands (Fig. 679 and 680). In size the breasts may vary from three or four times the normal to those reaching down to the knees; breasts extending to the umbilicus are not uncommon. Tumors within the breast causing enlargement must not be overlooked, and elephantiasis of the organ must be considered, especially in tropical countries.

A few instances of extensive hypertrophy of the breast in the male, *gynecomastia*, have been reported. The condition develops about pu-

[1] For a study of hypertrophy of the breast, see *Kirchheim, L.*, Arch. f. klin. Chir. (Langenbeck), 1902, lxviii, 582 (bibl.).

berty, and both sides are usually affected; it is occasionally accompanied by secretory activity. In some cases there has been an accompanying genital malformation which may have been the cause of the condition,

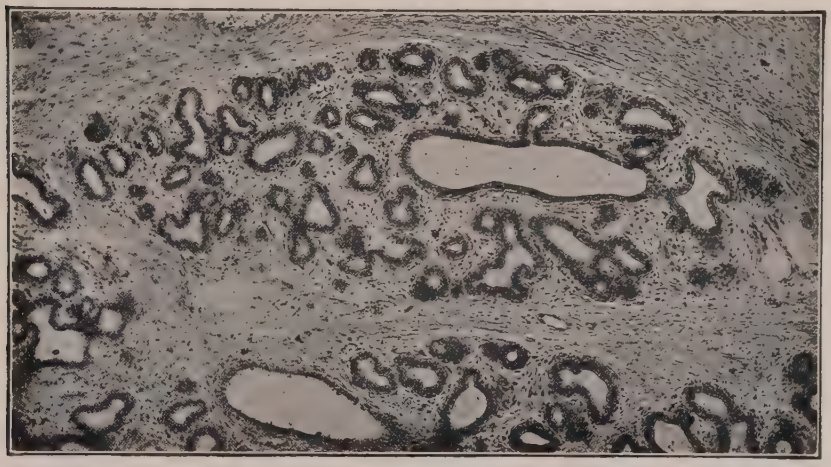


FIG. 679.—HYPERTROPHY OF MAMMA.
From case shown in Fig. 678. Low power, showing topography.

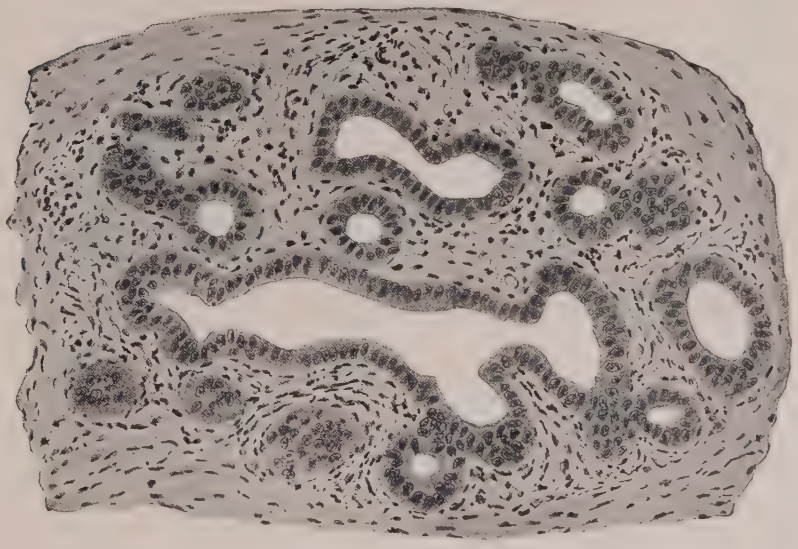


FIG. 680.—HYPERTROPHY OF MAMMA.
Showing structure of the enlarged breasts of Fig. 678.

or a disease of the endocrine glands, which affects all of the generative organs.[1]

[1] For a very extensive study of these and other lesions of the breast, see *Deaver, J. B.*, and *McFarland, J.*, The Breast: Its Anomalies, Its Diseases, and Their Treatment, Philadelphia, 1917. The book contains an extensive bibliography, but unfortunately many of the references are incorrectly given.

HEMORRHAGE.

In young women who suffer from amenorrhea or dysmenorrhea, small hemorrhages sometimes occur in the mammæ at the time of menstruation. The blood may find its way into the milk ducts and exude in small quantities at the nipple.

Contusions of the breast may produce extravasations of blood in the mammary gland or the surrounding connective tissue. The blood may be absorbed, or may remain and be surrounded by fibrous tissue, or may be converted into cysts.

A somewhat infrequent lesion of the breast is one in which the characteristic symptom is the discharge from the nipple of a serous or bloody

Fig. 681.—Papilloma of Duct Near Nipple Causing Serous Discharge.

fluid. The fluid appears spontaneously and may often be increased by pressure on the areolar area. The condition is most frequent in early adult life. In most instances the cause is a papillary growth in the ducts leading to the nipple. A tumor may not be discoverable, or a small nodule can be felt in the areolar area, or the breast may contain nodules of cyst-adenoma (see p. 1016), or one or more hard nodules may show that cancer is present. In the benign cases the fluid is pale yellow, odorless and rather thick and sticky in quality. In cyst-adenoma it is usually thicker, while in carcinoma it is more watery, darker in color, larger in amount, and often of a rather offensive odor. Spontaneous cessation of the discharge may occur or it may continue and a benign or malignant tumor develop later. Given such a discharge, it is important

to determine the nature of the underlying process. Statistics vary considerably. In one large series[1] the percentage of lesions with exudation was about the same, 6 per cent. In half of each type it was bloody, so no conclusions can be drawn from the kind of exudate as to the type of tumor. But looking at the matter from another aspect, 70 per cent. of the patients showing the symptoms have a benign growth[2] and most observers hold to the view that the presence of a serous or bloody discharge from the nipple of a non-lactating breast in a woman under forty-five years of age is evidence of a pathological lesion only; but the final diagnosis must be made from the physical signs attributable to either benign or malignant neoplasms. An exploratory operation, if necessary with a frozen section diagnosis, is the proper method, and will often obviate mutilating the patient.[3]

When the excised material is examined the duct leading from the nipple may have only a small tumor in its wall (Fig. 681), or the duct may be completely occluded by such a papillary growth, or the duct may be dilated and filled with papillary tumor. The whole process may be confined to a single duct and no other lesion may be present in the breast. In other instances a cystadenoma may be present with much chronic inflammatory material in the neighborhood of the duct, and in still other cases, and in a very small percentage indeed as a rule, there will be found a carcinomatous change shown by invasion of the breast connective tissue by elements of the papilloma. Under other circumstances the duct may contain a small bleeding papilloma while deeper in the breast, without any connection with the superficial process, there may be an extensive cyst-adenoma or carcinoma.

INFLAMMATION. (Mastitis.)

During lactation the nipple is liable to become inflamed, and ulcers and fissures may form.

There is a form of eczematous inflammation of the nipple and areola which tends to ulcerate and in which carcinoma may occur. This is known as Paget's disease (see page 1028).

Acute Exudative Inflammation (Mastitis).—This occurs most frequently during lactation, being seen in about 4 per cent. of all parturient women. Occasionally this condition occurs during pregnancy, also, and even in women who are neither pregnant nor nursing. The portal of infection is usually the nipple, though the organisms often present in the milk ducts may be responsible. The infectious agent may be brought to the breast by the saliva of an infant suffering from stomatitis. Hematogenous infections usually are seen in non-lactating breasts as complications of the infectious diseases. Metastatic abscesses of the breast may follow puerperal pelvic infections and gangrene has been noted as a sequel of mastitis complicating scarlet fever, though it also occurs in women after delivery.

[1] *Miller* and *Lewis*, Jour. Am. Med. Assn., 1923, lxxxi, 1651 (bibl.).
[2] *Erdheim*, Arch. f. klin. Chir., 1926, cxxxix, 366 (bibl.).
[3] *Hart*, Arch. Surg., 1927, xiv, 793; *Risak*, Wien. klin. Woch., 1926, xxxix, 544 (bibl.).

The process may involve the subcutaneous connective tissue, the gland itself, or the connective tissue between the gland and the wall of the thorax. The inflamed tissues are at first congested, swollen, hard, and painful. The inflammation often stops at this point, and resolution takes place if the retention of the milk be relieved and natural drainage of the gland tissue inaugurated; but occasionally it progresses to suppuration. If the inflammation involve the subcutaneous connective tissue the abscess may be superficial and may soon open through the skin. If the gland be involved one lobule after another may become affected (Fig. 682), so that successive abscesses are formed. If the connective tissue beneath the gland be inflamed, a deep abscess of large size may be formed which usually perforates through the skin, but sometimes into the pleural cavity. In both these latter forms of abscess there is apt to be necrosis of large portions of tissue. These abscesses may cica-

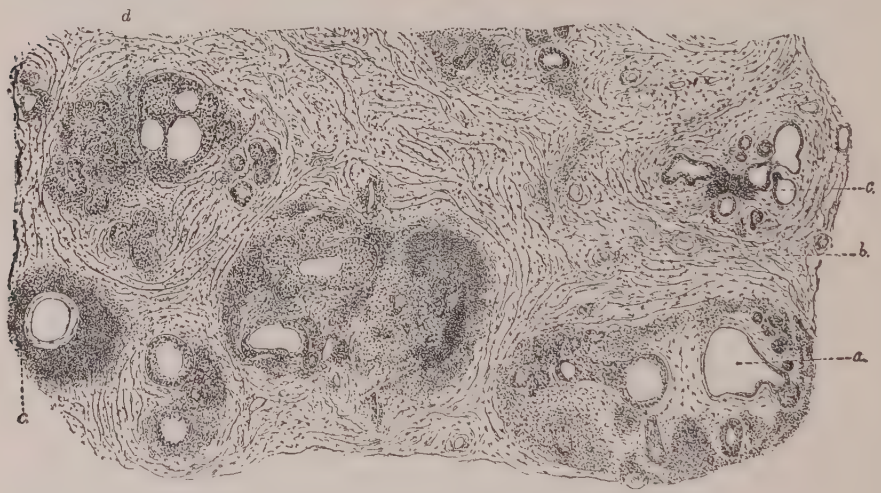


FIG. 682.—SUPPURATIVE MASTITIS IN NON-FUNCTIONATING GLAND.
a, Milk duct; *b*, interstitial tissue; *c*, dense collections of pus; *d*, diffuse infiltration of lobule with pus.

trize, or they may pass into a chronic condition and remain for a long time as suppurating, fistulous tracts. Suppurative mastitis when involving the glandular tissue is usually due to the presence of the Staphylococcus aureus or albus, less often to the presence of a streptococcus; when the interstitial connective tissue is affected the streptococcus is usually responsible.

In new-born children an acute mastitis may occur with painful swelling of the breasts, which usually subsides in a few days, but may go on to suppuration.

Acute exudative inflammation may occur in a gland which is already the seat of chronic inflammation, and chronic mammary abscesses may be formed.

Epidemic parotitis is sometimes complicated by mastitis.

Chronic inflammation of the interstitial connective tissue of the mammary gland may follow acute processes or be chronic from the

onset. It leads to the formation of dense connective tissue, which replaces the destroyed parenchyma of the gland, and may or may not be

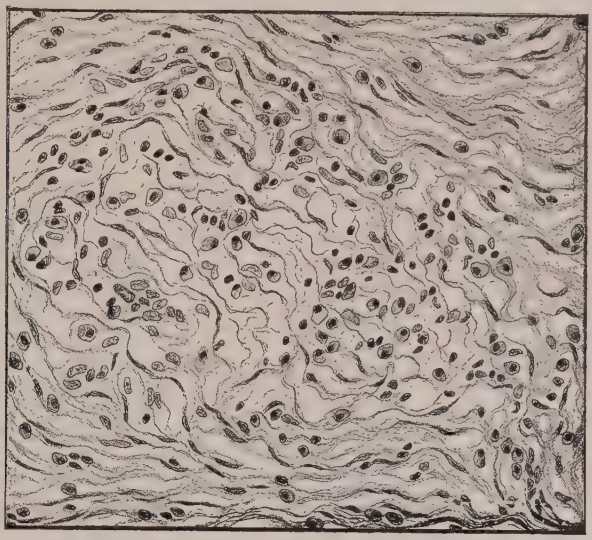


FIG. 683.—PLASMA CELLS AND LYMPHOCYTES IN BREAST IN CHRONIC MASTITIS.

FIG. 684.—GIANT CELLS FORMED ABOUT FATTY ACIDS AND CHOLESTERIN CRYSTALS IN CHRONIC MASTITIS.

Extensive lymphocytic infiltration surrounds the giant cells.

associated with cystic dilatation of the milk ducts and extensive atrophy of the glandular elements.

If the fibrous hyperplasia is excessive, cystic dilatation of the smaller ducts may extend throughout the organ owing to obliteration of the lumen by pressure.[1] Plasma and connective-tissue mast cells are often abundant in the interstitial tissue (Fig. 683). The collection of milk in the ducts or acini sets up irritative reactions (Fig. 684) and the separation of cholesterin in the contents of the broken down gland structures abets the process (Fig. 685). The epithelium may become atrophied or it may proliferate, and it frequently forms papillary projections into the dilated ducts. If this epithelial hyperplasia reaches any great extent it may be impossible to differentiate the lesions from a cystadenoma with secondary inflammation. This is the explanation of the confusion which long existed in regard to the nomenclature of the lesion. König,[2] considering the inflammation the most important, applied the name *chronic mastitis*, while Reclus[3] and others[4] thought that the glandular proliferative activi-

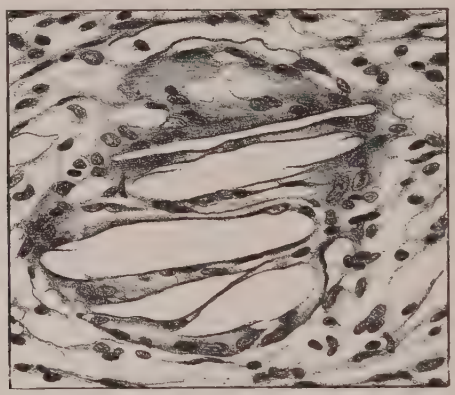


Fig. 685.—Giant Cells about Cholesterin Crystals in Chronic Mastitis.

ties were vital, and hence termed the disease *maladie cystique* or *cystadenoma* (page 1016).

Tuberculous inflammation of the mammary gland and its excretory ducts is of occasional occurrence. A primary infection of the breast, except in those rare cases in which the tubercle bacilli have gained entrance through abrasion of the nipple, is denied by most authorities. The majority of cases of infection are secondary to a lesion situated elsewhere in the body, reaching the breast through the blood-vessels or lymphatics. The infection may be manifested in the form of miliary tubercles, larger and smaller caseous masses of new-formed tissue, a diffuse tuberculous fibrosis resembling carcinoma, a direct inflammation,[5]

[1] *Ingier, A.*, Virchows Arch., 1909, cxcviii, 338.

[2] *König*, Centralbl. f. Chir., 1893, xx, 49. See, also, *Lichtenhahn, F.*, Deutsch. Ztschr. f. Chir., 1907, xc, 507.

[3] *Reclus, P.*, Rev. de chir., 1883, iii, 761; Gaz. d. hôp., 1887, lx, 673, 769.

[4] *Brissaud*, Arch. de physiol. norm. et path., 1884, iii, 99; *Schimmelbusch, C.*, Arch. f. klin. Chir. (Langenbeck), 1892, xliv, 117; *v. Saar, G.*, ibid., 1907, lxxxiv, 223; *Theile, P.*, ibid., 1908, lxxxviii, 261. For a study of this lesion with bibl., see *Greenough, R. B.*, and *Hartwell, H. F.*, Jour. Med. Research, 1903, N. S. iv, 416; and *Bloodgood, J. C.*, Surg., Gynec., and Obst., 1906, iii, 721.

[5] *Halstead, A. E.*, and *Le Count, E. R.*, Ann. Surg., 1898, xxviii, 685.

or cold abscesses.[1] Fistulous connections with the breast or axillary node lesions occur in the late stages. Microscopically the lesions show no important differences from tuberculosis elsewhere in the body.

A few cases of tuberculosis with adenoma or carcinoma of the breast have been reported, but the association is rare (Fig. 686).[2] The possibility of a retrograde transport of the bacilli from the axillary lymph-nodes has been suggested.[3]

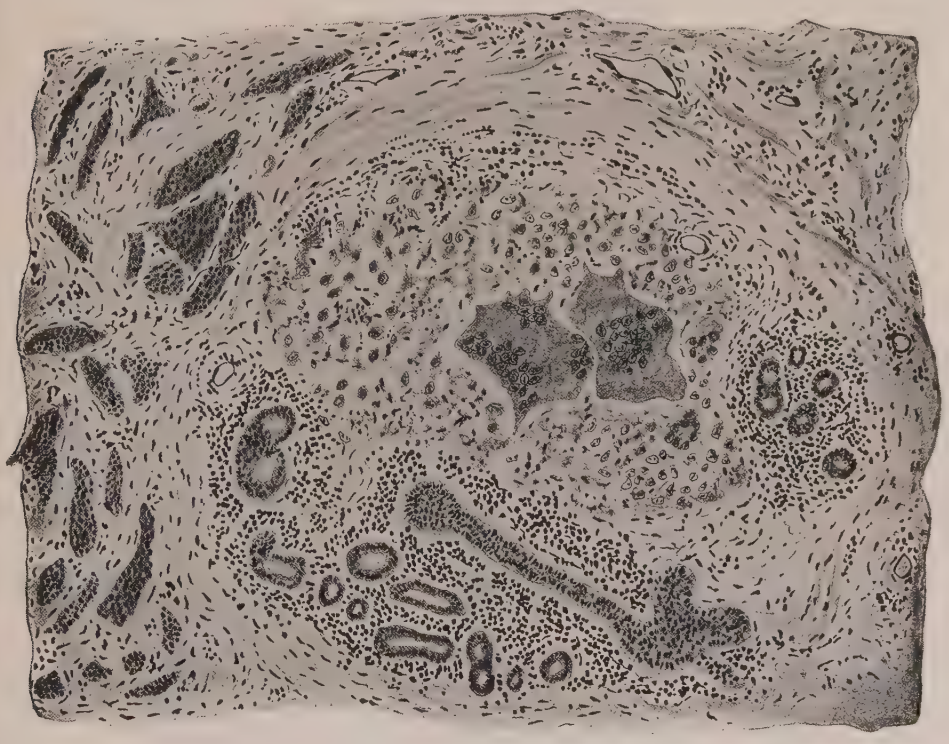


Fig. 686.—Carcinoma and Tuberculosis of Mamma.
The occurrence of these lesions together is unusual.

Syphilis of the breast[4] may occur as chancres, mucous patches, or gummata In very rare instances, the syphilitic process may consist only of a diffuse lymphocytic exudate with perivascular condensations, with accompanying endarteritis and swelling of the capillary endothelium. Such areas may be very hard, and the writer (Wood) has seen two specimens which had been excised for carcinoma.

Actinomycosis[5] may occur as a primary lesion of the breast, the infection gaining entrance probably through abrasions. It is seen also

[1] *Scudder, C. L.*, Am. Jour. Med. Sc., 1898, cxvi, 75.
[2] *Warthin, A. S.*, Am. Jour. Med. Sc., 1899, cxviii, 25 (bibl.).
[3] *Bundschuh, E.*, Zieglers Beitr., 1914, lvii, 65.
[4] *Deutsch, K.*, Wien. klin. Wchnschr., 1909, xxii, 127.
[5] *Sehrt, E.*, Beitr. z. klin. Chir. (Bruns), 1907, lv, 589: *Risel*, Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 322.

following actinomycosis in other situations, in the pleura, for example, and probably reaches the breast through the lymphatics. The characteristic sulphur yellow granules may be found in pus from the lesions.

A few cases of **sporotrichosis** have been reported.[1] The disease is caused by a spore-bearing mycelium which reaches the breast through the nipple by metastasis. An inflammatory area is found at the portal of entrance, and an abscess which contains polymorphonuclear leucocytes and large phagocytes forms in the center; surrounding this there is an area composed of inflammatory tissue with tubercle-like formation. In the pus from the abscess the mycelium may be demonstrated by suitable stains.

Sprue.—This fungus may develop in the tissue of the nipple in nursing women.

TUMORS.

Fibroma.—Circumscribed tumors composed solely of dense connective tissue are very rarely found in the breast. In the nipple they occur,

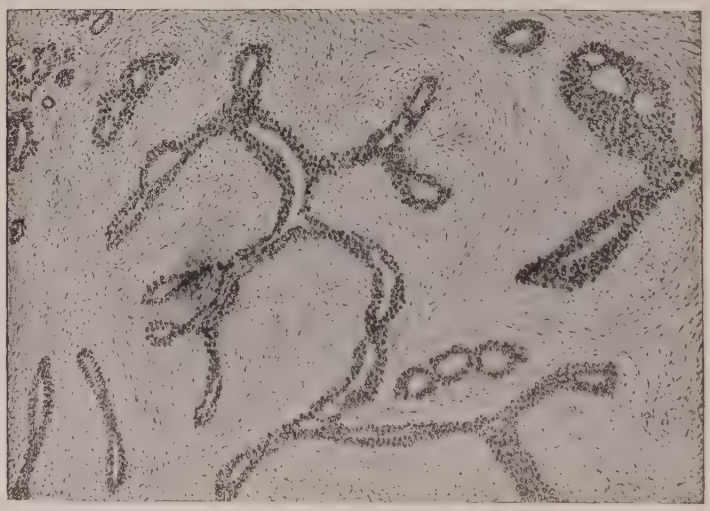


FIG. 687.—INTRACANALICULAR FIBROMA OF MAMMA.

but very infrequently.[2] In the usual type of fibroma the gland ducts and acini form a portion of the tumor.

Intracanalicular Fibroma.—These tumors are formed by a diffuse proliferation of loose connective tissue, and a growth of polypoid fibrous tumors from the walls of the milk ducts into their cavities, leading to dilatation. The glandular acini may be atrophied, or enlarged, or cystic. A section of such a tumor looks like a solid mass of fibrous tissue, divided by clefts and fissures lined with cylindrical or cuboidal epithelium (Fig. 687), or fibrous tissue containing cysts into which project polypoid fibrous

[1] *Quenu*, Rev. de chir., 1914, xli, 585.
[2] *Creite*, Deutsch. Ztschr. f. Chir., 1911, cix, 199.

outgrowths from the walls. Sometimes the new-formed fibrous growths into the dilated ducts are adenomatous in character, containing many new-formed irregular acini (Fig. 688). Such tumors may be called

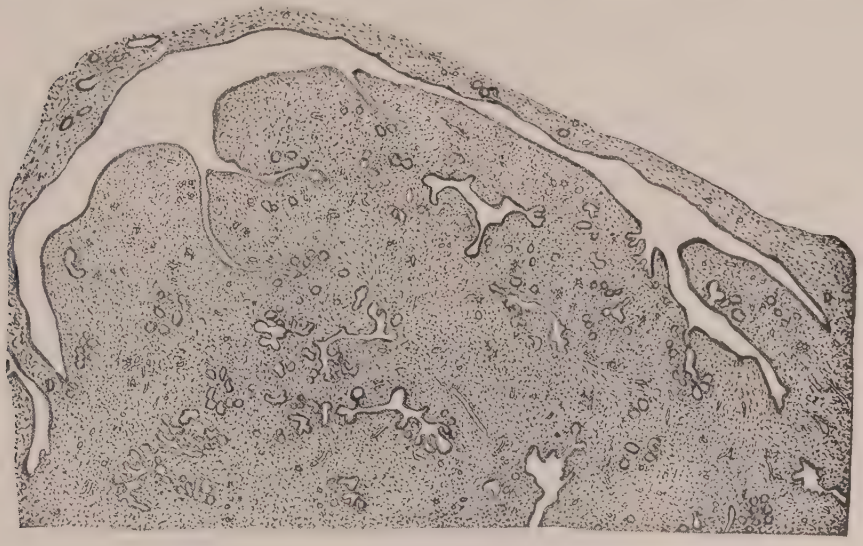


Fig. 688.—Intracanalicular Fibroadenoma of Mamma.
Showing new-formed gland acini in the fibrous-tissue mass growing into a duct.

Fig. 689.—Pericanalicular Fibroma of Mamma.

intracanalicular fibroadenomata. These tumors grow slowly, but if left to themselves may reach an enormous size. The skin over them may ulcerate and the tumor project through the opening in fungous masses.

They may be associated with interstitial fibrous hyperplasia of the gland, and sarcoma occasionally develops in them.[1] Wandering cells of various types are formed in the connective tissues, especially plasma cells and connective-tissue mast cells. There may be much mucoid material between the collagen fibers. The fat cells also may join in the hyperplasia, forming large multinucleated cells which have lead to an erroneous diagnosis of sarcoma or tuberculosis.

Pericanalicular Fibroma.—Sometimes the new connective tissue forms a more or less thick cylindrical investment of the duct without growing into its lumen. This formation (Fig. 689) is sometimes called *pericanalicular fibroma.*

Cystadenoma.[2]—This form of breast tumor is of great clinical importance as not infrequently it forms the starting point for carcinoma. It has been variously called *chronic cirrhosing mastitis* (Billroth), *chronic*

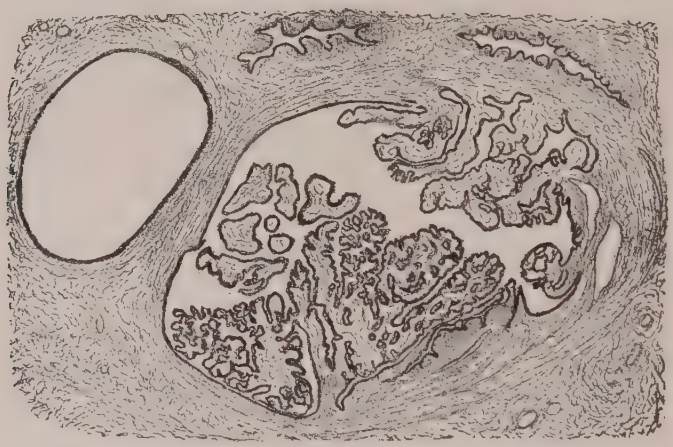


Fig. 690.—Papillary Cystadenoma of Mamma.

interstitial mastitis (Bryant), *cystadenoma* (Schimmelbusch), *cystic disease of the breast* (Reclus), and *chronic cystic mastitis* (König). This complexity of nomenclature has been previously mentioned (page 1012) as due to the fact that the lesion varies greatly from case to case.

These tumors are most frequent about the time of the menopause, but they may occur before the age of twenty. Grossly, the breasts are usually not greatly increased in size, but one or often both may be more or less filled with a flat cake-like hard mass, on the surface of which are often palpable small elastic masses which are thin-walled cysts. These cysts may occupy a large part of the breast, or the breast may be extremely firm and hard with or without very minute cysts. Large or small papillary outgrowths may more or less fill the cysts. When the papillary growths form a large part of the tumor mass, the name *papillary*

[1] *Speese*, Ann. Surg., 1910, li, 212; *Prym*, Frankfurt. Ztschr. f. Path., 1912, x, 60.

[2] *Tietze*, Deutsch. Ztschr. f. Chir., 1904, lxxv, 117; *Berka*, Zieglers Beitr., 1912, liii, 284; *v. Saar*, Arch. f. klin. Chir. (Langenbeck), 1907, lxxxiv, 223 (bibl.).

cystadenoma is employed (Fig. 690). The tumor may be solid throughout or may be composed of discrete nodules.

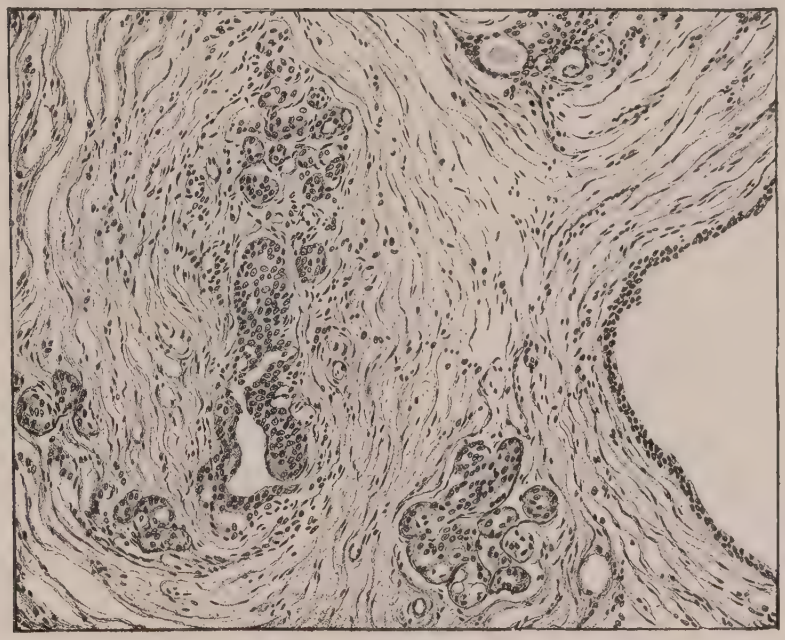


FIG. 691.—CYSTADENOMA OF MAMMA.
Showing masses of epithelium in the alveoli, and small cysts.

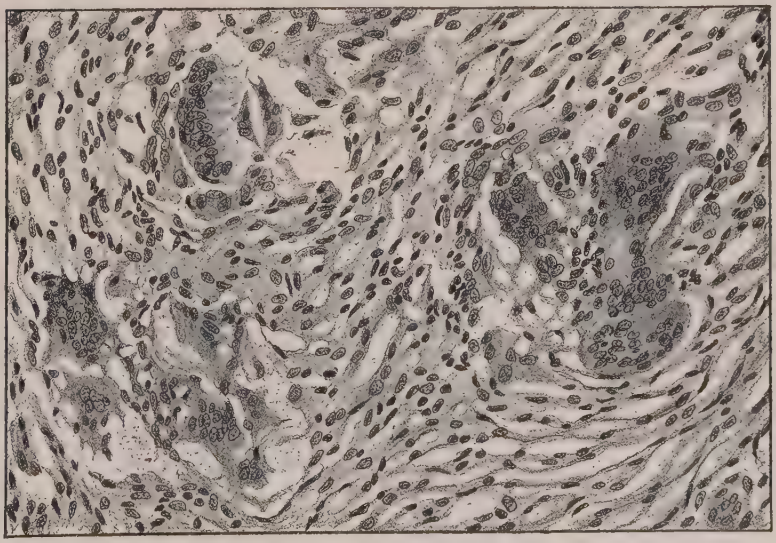


FIG. 692.—GIANT CELLS AND CONNECTIVE-TISSUE REACTION IN CYSTADENOMA OF BREAST.

The connective tissue may be dense and fibrous with very few nuclei; it may be infiltrated with cells of lymphoid type (Fig. 691); rarely it may

FIG. 693.—ADENOMATOUS TYPE OF GLAND WITH A FEW SMALL CYSTS.
Senile type of cystadenoma.

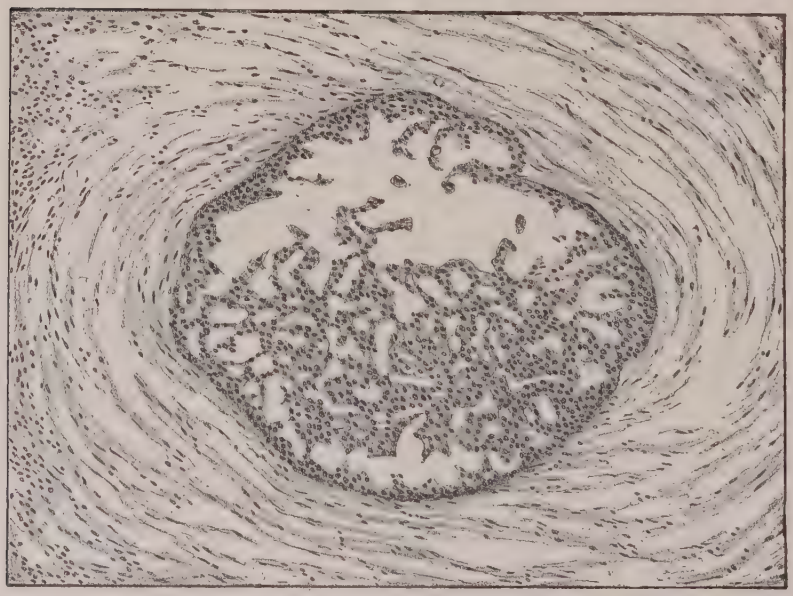


FIG. 694.—CYSTADENOMA OF MAMMA.
Papillary outgrowths of epithelium in dilated glands.

show mucoid degeneration. When the inflammatory phase of the growth is predominant, the free fat and fatty acids from the retained milk give rise to extensive cellular reactions of either spindle-cell or lymphoid-cell type with giant-cell formation. Such lesions are often erroneously considered as tuberculous (Fig. 684 and 692). The morphology of the epi-

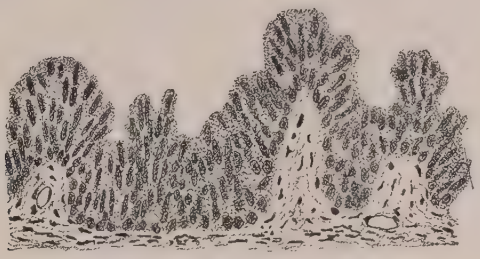


FIG. 695.—CYSTADENOMA OF MAMMA.
Wall of acinus lined with duct epithelium.

thelium is most variable, covering all varieties between the adenomatous type with glands not far from normal, some of which properly belong to senile involution changes (Fig. 693); glands having a number of layers of epithelium such as are frequently found in senile breasts; glands dilated with papillary projections of epithelial cells from the walls (Fig.

FIG. 696.—CYSTADENOMA OF MAMMA.
Extensive hyperplasia of the lining epithelium of the glands, but without breakdown of the basement membrane.

694 and 695); and, finally, glands which are entirely filled with solid masses of epithelium (Fig. 691). While these masses are very suggestive of carcinoma, they can usually be distinguished by the fact that the nuclei are not hyperchromatic and show no mitoses, and that the cells do not pass beyond the basement membrane into the surrounding tissues

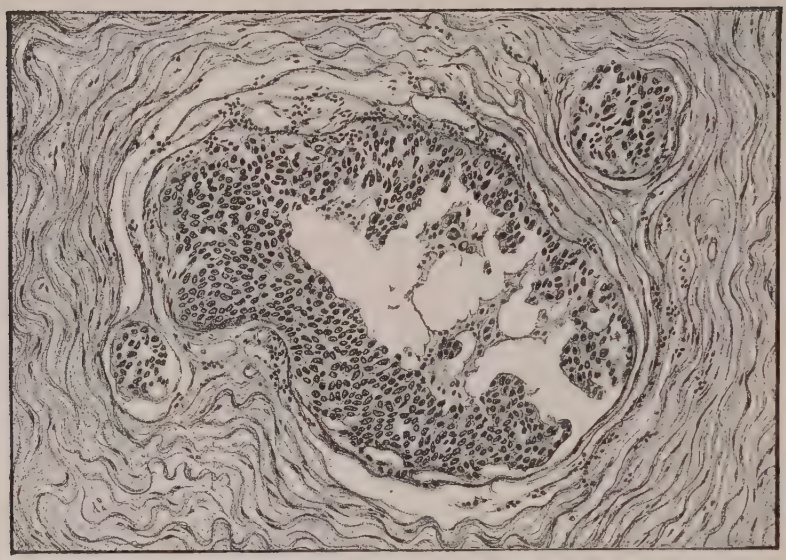


FIG. 697.—CYSTADENOMA OF MAMMA.
Proliferation of the epithelium lining the ducts, with slight inflammatory reaction surrounding the altered glands.

FIG. 698.—FIBROADENOMA OF MAMMA, VERY CELLULAR, RESEMBLING DIFFUSE CARCINOMA OR SARCOMA.

(Fig. 696 and 697). When there is much inflammation, however, the sharp outline of the membrane is often obliterated and the cells look as though they were invading the surrounding tissues; but even this picture may be seen in tumors which are still benign. The only certain evidence

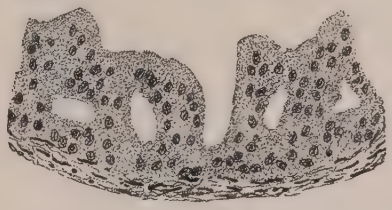


Fig. 699.—Cystadenoma of Mamma.
Wall of acinus lined with irregular epithelial cell masses.

of malignancy is the presence of cells as individuals or groups in the connective tissue at a considerable distance from the gland in question.

Occasionally one will meet with a tumor of this type in which cells greatly resembling cancer cells are found distributed throughout the connective tissue (Fig. 698). On careful inspection, however, these are

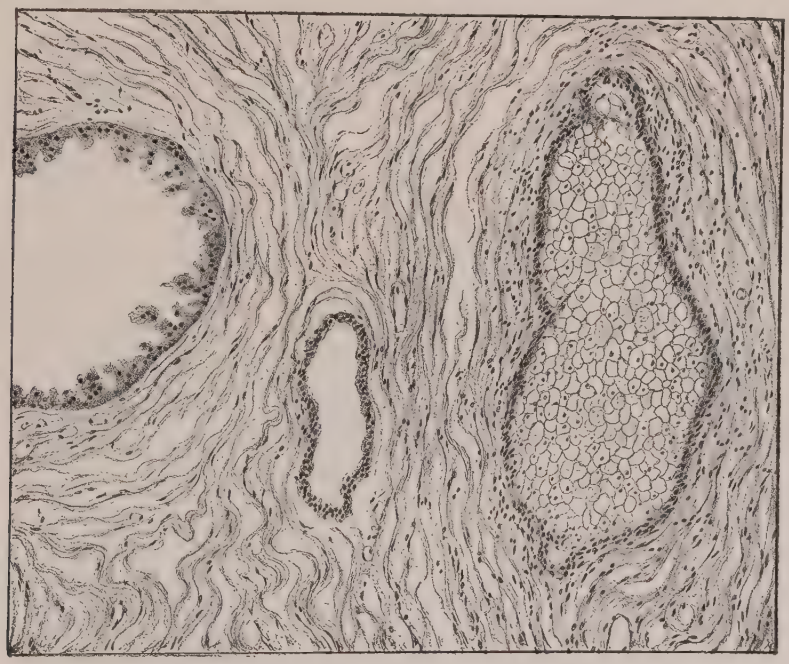


Fig. 700.—Colostrum Cells Filling Duct in Cystadenoma of Mamma.

found to resemble more closely the connective-tissue cells or endothelial cells. The writer (Wood) has seen a number of such suspicious cases in which no axillary involvement was found, and no recurrence followed simple operative removal of the tumor, which is some evidence, though not final proof, that the growth was not carcinomatous.

Another type of cyst has been considered either as lined with duct epithelium or as derived from sweat glands[1] (Fig. 699).

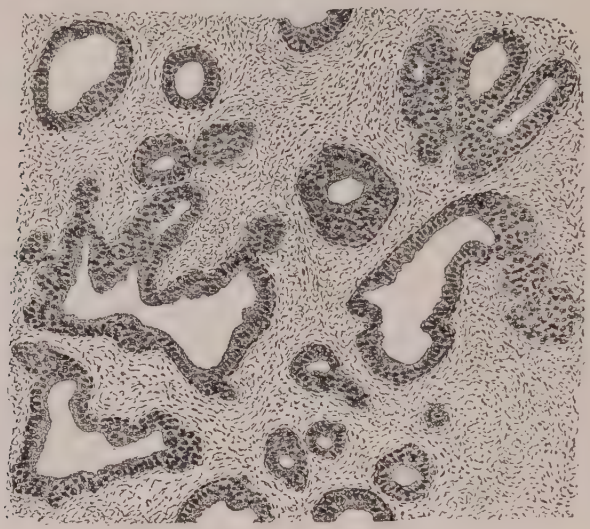


FIG. 701.—ADENOMA OF MAMMA.
These new-formed acini, while maintaining the gland character, are still quite atypical in form and grouping and in the irregularity of the epithelium.

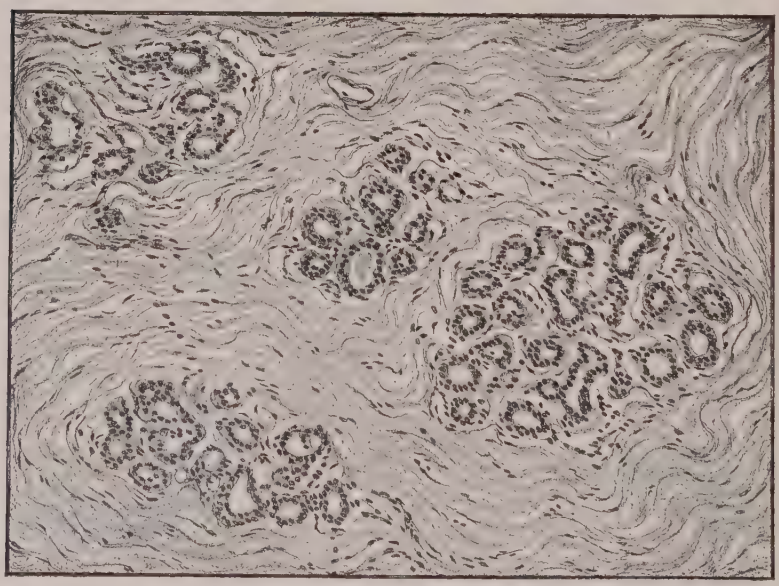


FIG. 702.—ADENOMA OF MAMMA.

[1] *Krompecher, E.*, Zieglers Beitr., 1908, xliv, 51, 88; Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 365; *v. Saar*, Ergebn. d. Chir. u. Orthoped., 1910, i, 413, also believes that they have their origin in the sweat glands.

In this type of cyst also there may be budding of the lining epithelium (Fig. 700). The wall is lined with high cylindrical epithelium which takes a deep stain with eosin and has a small nucleus, rather poor in chromatin. The cells are entirely different in appearance from those of the glands of the breast. There may be papillary projections into the lumina, also.

A third form is occasionally seen, in which the gland is entirely filled with large foam or colostrum cells (Fig. 700), evidently derived from the wall of the gland and corresponding to the milk cells of the secreting breast; in some instances they may be cells in which lipoid material has developed during the course of degeneration.

A case of cystic adenoma with ciliated epithelium has been described.[1]

Adenoma and **fibroadenoma** are composed of glandular acini and ducts surrounded by connective tissue, and are the most frequently occur-

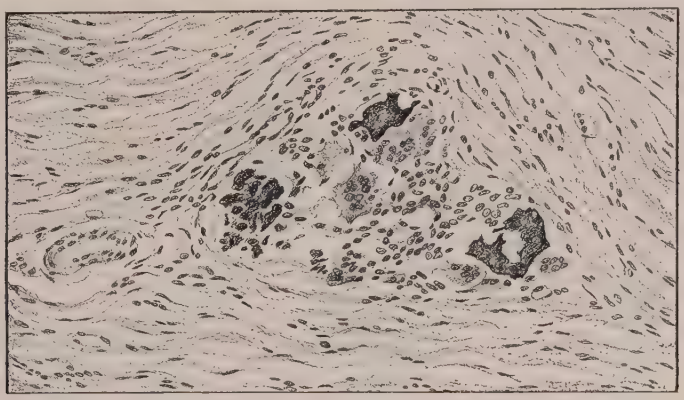


Fig. 703.—Calcification of Inflammatory Exudate in the Breast with Foreign Body Giant Cells.

ring growths of the mamma (Fig. 701 and 702). These tumors are usually referred to as fibroadenoma,[2] for a pure adenoma composed only of glandular tissue is of rare occurrence.[3] They are either single or multiple, or several may be developed successively in the same breast. They grow, as a rule, at first slowly, afterward more rapidly. Their structure may be further complicated by the dilatation of one or more of the ducts which compose the tumor into cysts, and the ingrowth of connective tissue from the walls of these cysts.

Myxoma.—This may be a circumscribed growth replacing part of the mamma, or it may form in the same way as the intracanalicular fibromata. It is composed of a fibrous connective tissue filled with mucin. True myxomata of the breast are uncommon, but in the intracanalicular tumors there may be found a combination of fibrous, mucous, and sarcomatous tissue (*adenomyxosarcoma*).

[1] *Buday, K.*, Virchows Arch., 1899, clvi, 395.
[2] *Berka*, Zieglers Beitr., 1912, liii, 284.
[3] *Kuru, H.*, Deutsch. Ztschr. f. Chir., 1909, xcviii, 415.

Osteoma and **chondroma** are rare forms of tumors in the mamma. The osteomata may consist of osseous tissue alone or may contain bone-marrow. Chondromata may consist solely of cartilaginous tissue, or of both bone and cartilage, *osteochondroma.*[1] The origin of such heterologous masses is generally assumed to be due to metaplasia of the connective tissue, but may be explained also as a congenital dislocation of embryonic structures from the ribs. Calcification of inflammatory tissue must be distinguished from true bone formation (Fig. 703).

Lipoma consists of adipose tissue, and may be intraglandular or extraglandular. Unusually large tumors of the breast have been reported, weighing up to twenty-five pounds. The tumors may be bilateral; and

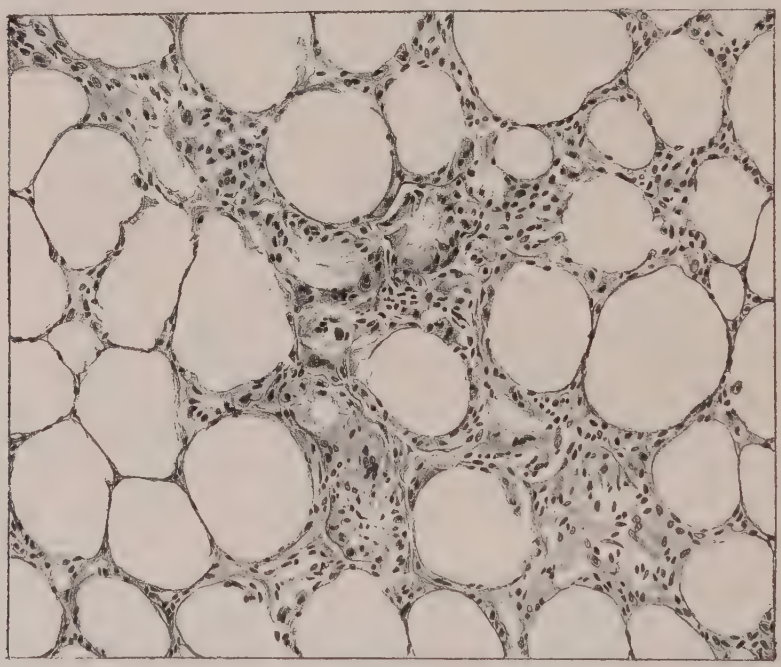


FIG. 704.—FAT TUMOR OF BREAST FOLLOWING BLOW.
The tumor is largely composed of newly formed fat cells, cholesterin crystal and fatty acid giant cells.

they may also be multiple, and are, as a rule, encapsulated. They are often mistaken for cysts owing to the fluctuation noticeable on palpation.

After a blow an inflammatory reaction may be set up in the fat tissue of the breast with active regeneration of fat, and the formation of a considerable mass of firm tissue which has been mistaken, even microscopically, for carcinoma[2] (Fig. 704).

Myoma[3] may arise from the muscle cells found in the nipple.

Angioma of the mammary gland may be composed of blood-vessels or lymph-vessels, though the latter type is very rare.

[1] *Cornil*, Les Tumeurs du Sein, Paris, 1908.
[2] *Lee* and *Adair*, Ann. Surg., 1920, lxxii, 188.
[3] *Lindfloss*, Monatschr. f. Geburtsh. u. Gynäk., 1900, xi, 763.

Sarcoma of the breast[1] is rare, being estimated to form only 2 to 3 per cent. of all breast tumors. The neoplasms are sometimes limited, tending to displace the gland rather than to infiltrate it; or they may develop in a nodular or diffuse form, so that the entire gland may be replaced by the growth; in other cases the sarcoma may arise in intracanalicular growths. The tumors are composed most frequently of round or spindle cells; the giant-cell types are rare (Fig. 705). When the growths become large they often ulcerate. Metastasis in the axillary lymph-nodes, while it does occur, is very infrequent, the usual path being through the blood-vessels, as with sarcoma in general.

Among the rarer types of sarcoma are the *melanosarcomata*, the richly vascular *angiosarcomata*, *chondrosarcomata*,[2] and *osteoid sarcomata*,[3] as

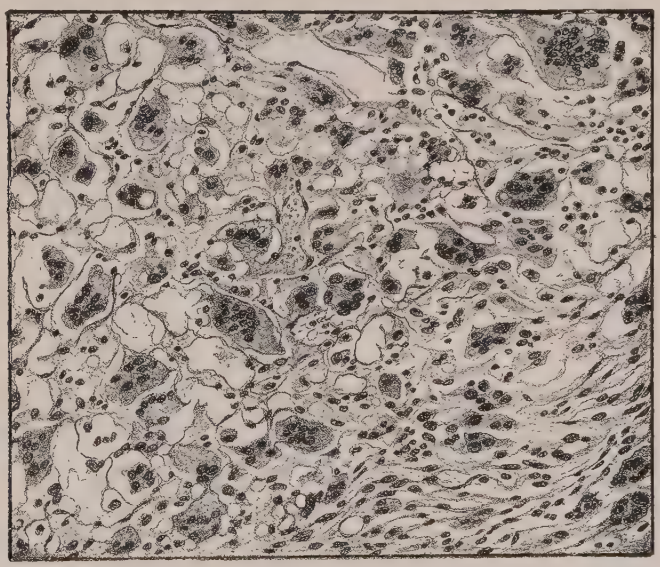


Fig. 705.—Sarcoma of Mamma, giant-cell Type.

well as *complex tumors* containing muscle fibers, and *carcinosarcomata*, either as separate tumors[4] or mixed.[5]

Cholesteatomata have been occasionally found;[6] and **chloromata** and **leukemic tumors**[7] of the breast have been reported as secondary deposits.

Carcinoma of the mamma is most common in women between the ages of thirty-five and fifty-five, as is sarcoma, though it has been reported as early as the eleventh year and also in very elderly persons. It is more

[1] *Finsterer, J.*, Deutsch. Ztschr. f. Chir., 1907, lxxxvi, 352; *Rohdenburg, G. L.*, Proc. New York Path. Soc., 1917, xvii, 112.

[2] *St. Arnold*, Virchows Arch., 1897, cxlviii, 449 (bibl.).

[3] *Stilling*, Deutsch. Ztschr. f. Chir., 1881, xv, 247; *Hueter* and *Karrenstein*, Virchows Arch., 1906, clxxxiii, 495; *Sehrt*, Beitr. z. klin. Chir. (Bruns), 1907, lv, 574.

[4] *Schlagenhaufer*, Centralbl. f. allg. Path., 1906, xvii, 385.

[5] *Orth, J.*, Charité-Ann., 1910, xxxiv, 357; *Krompecher, E.*, Zieglers Beitr., 1908, xliv, 88 (bibl.).

[6] *Konjetzny, G. E.*, Beitr. z. klin. Chir. (Bruns), 1912, lxxviii, 504; *Stoerk* and *Erdheim*, Wien. klin. Wchnschr., 1904, xvii, 358.

[7] *McWilliams, C. A.*, and *Hanes, F. M.*, Am. Jour. Med. Sc., 1912, cxliii, 518.

frequent in the unmarried. While it occurs in either breast, though in the right rather more frequently than in the left, it is rare that both

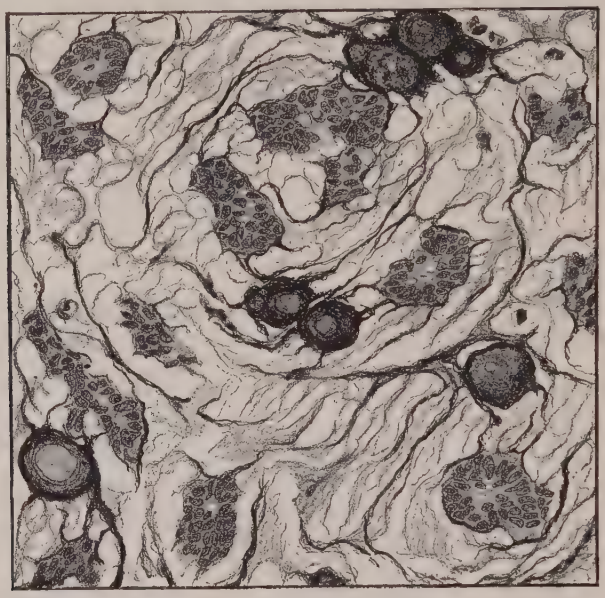


FIG. 706.—GELATINOUS CARCINOMA OF MAMMA WITH LAMINATED CALCIFIED MASSES SCATTERED THROUGH THE TUMOR.

FIG. 707.—LYMPHOID INFILTRATION ABOUT ALVEOLI OF A SLOW GROWING KERATINIZING CARCINOMA OF MAMMA.

breasts are involved. Carcinoma of the male breast forms about 2 per cent. of all mammary carcinomata.

Carcinoma generally begins as a small circumscribed nodule, situated

most frequently in the upper outer quadrant of the gland. The cells may remain confined to the alveoli for a time and invasion of the surrounding connective tissue, lymphatics, and veins may occur late. Such outgrowths may, however, occur very early when the tumor is small, occasionally not more than a centimeter in diameter, and extensive invasion of the nodes may be an early occurrence also. The cells of the tumor may be small or large; they may keratinize. The adenomatous type is not frequent, but may metastasize into the nodes and preserve its morphology. The squamous-cell type arises most often in the nipple or from the ducts. Its metastases also are of squamous keratinizing cells. The gelatinous form may calcify (Fig. 706).

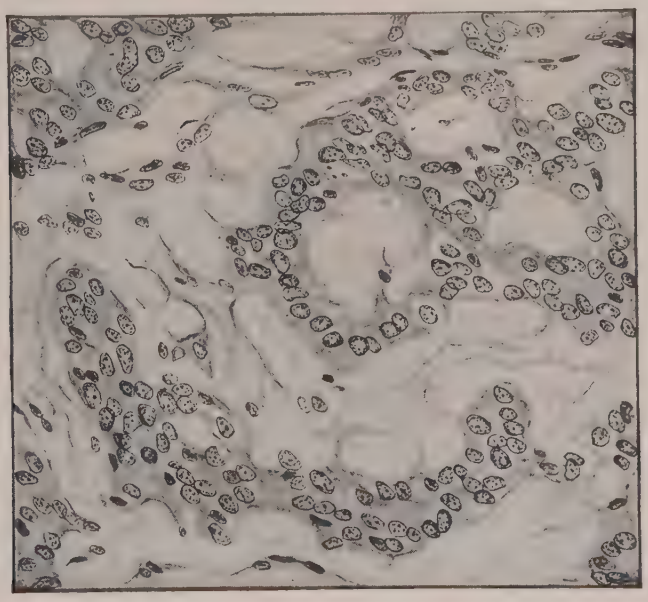


Fig. 708.—Gelatinous Carcinoma of Mamma (Carcinoma Myxomatodes). Of ten years' duration without metastasis.

Lymphoid infiltration of the fibrous tissue of the breast is most frequent and extensive in the slow growing types (Fig. 707), and may be absent in the medullary forms. Mucoid degeneration of the connective tissue is often seen.

The tumor enlarges and involves more and more of the breast. Sometimes it is diffuse from the first, and sometimes it begins in the nipple. All the adjacent tissue may become infiltrated including the axillary and cervical nodes. The axillary nodes may be involved very early and by the end of a year are almost invariably the seat of disease, and from here metastatic tumors are formed in different parts of the body.[1] The ex-

[1] For a study of dissemination of carcinoma of the breast, see *Stiles, H. J.*, Brit. Med. Jour., 1899, i, 1452; and *Handley, W. S.*, Cancer of the Breast, London, 1906.

tension of carcinoma may take place by transference of the cells through the main lymph-channels, by growth or ameboid wandering of cells along the smaller lymphatic vessels, and by way of the blood-stream.

The *medullary* form of carcinoma is the most malignant, next in order of malignancy being *carcinoma simplex, scirrhus, adenocarcinoma,* and *squamous-cell* and *colloid* or *gelatinous carcinoma.* Unfortunately, the colloid or gelatinous type, the least malignant (Fig. 708), is also the most rare, occurring in about 1 per cent. of all cases, while the medullary and the carcinoma simplex forms are the most common. The relative rate of metastasis formation seems to be dependent somewhat upon the

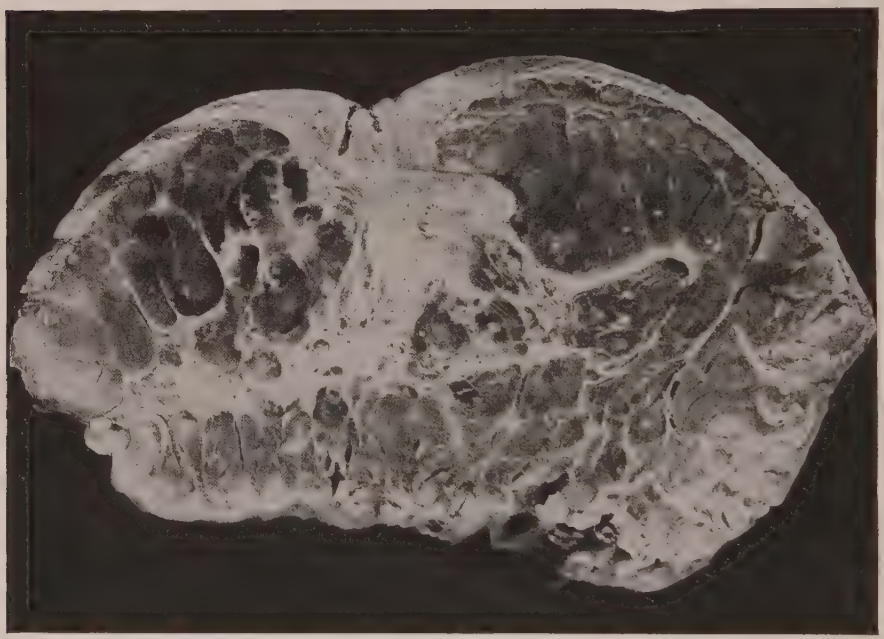


Fig. 709.—Carcinoma of Mamma—Fibrous Type—Scirrhus.

The nipple is retracted by the shrinkage of the fibrous tissue. The growth is extending along the fibrous bands of the mammary fat and at the left has reached the plane of excision. The darker portions in the figure are lobules of fat.

size of the cells, a small-cell scirrhus (Fig. 709) metastasizing much earlier and more extensively than a large-cell medullary carcinoma.

Cancer en cuirasse is a condition in which there is extensive superficial involvement of the chest, shoulder, and arm with carcinoma.

Paget's disease[1] is an eczema around and involving the nipple, which it eventually destroys. When it has existed for a long period, it is commonly followed by squamous or glandular carcinoma in the neighboring breast tissue. Many of the cases clinically diagnosticated as Paget's disease and treated disastrously with salves or radiation, are actually from the beginning either carcinomata of the ducts leading to the nipple

[1] *Jopson, J. H.,* and *Speese, J.,* Ann. Surg., 1915, lxii, 212.

with secondary invasion of the skin, or primary epitheliomata of the areola; in fact, the opinion is gaining ground that the eczema is in many instances secondary to a slow growing carcinoma arising from the ducts.[1] Microscopically the tumor cells are often found to have invaded the lymph-channels at the base of the epidermis and there given rise to pictures which have been mistaken for parasites.

All cases of chronic eczema of the nipple which do not heal after a few weeks' treatment should be considered carcinomata.

Cysts of the mamma seem to be for the most part retention cysts, formed by the dilatation of the gland ducts or acini. During lactation such retention cysts are sometimes formed, and then contain milk.[2] If retained for a long period the milk becomes inspissated to form a yellowish greasy mass, the so-called butter cysts of the breast.[3] They may reach an enormous size. At other times retention cysts are formed containing serous or viscid, brownish fluid, which often exudes through the nipple. These cysts may be large or small, single or multiple. There are usually at the same time some growth and induration of the connective tissue of the gland. In some cases there are polypoid outgrowths of connective tissue from the wall of the cyst. These cysts are not to be confounded with the cysts which are developed with the intracanalicular tumors, described above.

Sebaceous cysts, dermoid cysts, and hydatid cysts of the breast have been described.[4]

FEMALE SEX HORMONE.

The female sex hormone is secreted by the growing follicle, the corpus luteum and the placenta, is poured out into the circulation, and exerts a specific stimulation upon the Mueller's tract (vagina, uterus and tubes) as well as upon the breasts, preparing these organs to subserve their function of reproduction. Thus many of the morphological alterations described in this chapter depend wholly upon the action of this hormone, and a résumé of its nature and function should properly be included in a work of this nature.

This is the only hormone which has been demonstrated in the circulating blood by a direct and specific test.[5] It therefore supplies the final proof of the soundness and correctness of the hormone theory. While sex itself appears to be a chromosomal quality predetermined at the time of conjugation of the male and female elements, the elaboration of all further sexual development is governed by the secretion of the gonads.

During infancy and prepuberty the amount of hormone secreted is minimal, sufficient only to keep the growth of the sexual organs (including the breasts) up to that of the rest of the body. With the onset of puberty, which can be initiated artificially at any time by giving sufficient

[1] *Handley, W. S.*, Lancet, 1917, i, 519.

[2] *Nordmann, A.*, Virchows Arch., 1897, cxlvii, 475.

[3] *Rogowitsch, N.*, Zieglers Beitr., 1895, xviii, 487; and *Samelson-Kliwansky, L.*, Virchows Arch., 1905, clxxix, 76. For an analysis of the fat content of these cysts, see *Wells, H. G.*, Chemical Pathology, Philadelphia, 1918, p. 515.

[4] For a study of cysts of the breast, see *Bloodgood, J. C.*, Bull. Johns Hopkins Hosp., 1907, xviii, 139.

[5] Demonstration of the Female Sex Hormone in the Circulating Blood, *Frank, R. T., Frank, M. L., Gustavson, R. G.*, and *Wyerts, W. W.*, Jour. Am. Med. Assn., 1925, lxxxv, 510.

female sex hormone parenterally, and which then appears to continue spontaneously,[1] throughout the sexual life of the female, the ovary secretes an amount of hormone varying at different parts of the cycle. By comparing the ovarian, the uterine, and the circulatory cycle, an accurate picture of what is going on can be obtained.

The Ovarian Cycle.—The follicle fluid of the maturing follicle contains a concentrated amount of female sex hormone.[2] The corpus luteum likewise contains the hormone but gives it up to the circulating blood almost as rapidly as formed so that the hormone is only stored in the yellow body just at the period at which involution of the blood-vessels takes place.[3]

The Uterine Cycle.—At the time that the ovary contains only immature follicles, the uterus is in a stage of rest. About midway between two periods, when ovulation takes place and when the follicle fluid is poured out into the pelvic peritoneal sac, a rapid increase of activity of the endometrium is noted with hyperplasia of the glands and stroma, mitosis of the epithelium, secretion and turgescence. This process continues and is accentuated up to the time of menstruation which corresponds, as we know from physiological studies, to the time when the corpus luteum involutes. Then takes place menstruation, abruptly, with exfoliation of the decidua of menstruation, the process coming to a climax with the out-pouring of the menstrual blood.

Circulatory Cycle.—From the second day of menstruation to approximately ten days before the next expected period, no female sex hormone can be detected by the Frank-Goldberger technic.[4] From then on an increasing amount of female sex hormone is found in the circulating blood. With the onset of the menstrual bleeding the hormone disappears from the blood and is found in great concentration in the menstrual fluid.

In case of impregnation, the female sex hormone is no longer found in the circulation and can not be demonstrated until about the tenth to the twelfth week of pregnancy, after which time it is found throughout pregnancy in considerable concentration until the onset of labor.

[1] The Female Sex Hormone. An Analysis of Factors Producing Puberty, *Frank, R. T., Kingery, H. M.*, and *Gustavson, R. G.*, Jour. Am. Med. Assn., 1925, lxxxv, 1558.

[2] The Ovary and the Endocrinologist, *Frank, R. T.*, Jour. Am. Med. Assn., 1922, lxxviii, 181.

[3] The Female Sex Hormone and the Gestational Gland, *Frank, R. T.* and *Gustavson, R. G.*, Jour. Am. Med. Assn., 1925, lxxxiv, 1715.

[4] The Female Sex Hormone. VI. Demonstration of the Female Sex Hormone in the Human Blood: Technic: Clinical Applicability, *Frank, R. T.* and *Goldberger, M. A.*, Jour. Am. Med. Assn., 1926, lxxxvii, 1719.

CHAPTER XI.

REPRODUCTIVE ORGANS OF THE MALE.

The Penis.

Malformations.[1]

The penis may be absent with great defects of development of the rest of the body. The urethra then usually opens into the rectum. In rare instances a double penis is present.

An abnormally small penis may be associated with absence or arrested development of the testicles. The prepuce may be rudimentary or absent.

Congenital phimosis is not uncommon.

Hypospadias is an arrest of development of the penis and scrotum. In its highest degree the penis is short, the glans penis small. On the lower side of the penis is a deep cleft lined with mucous membrane, into which the urethra opens at the root of the penis. The scrotum remains separated into two parts, resembling labia majora. The testes may descend into their proper position on each side or remain in the abdomen. If the testicles continue to develop normally the individual has the appearance and capacities of a man; if their development is arrested the individual is apt to be of feminine type.

In lesser grades of hypospadias the two parts of the scrotum are joined and the penis is larger, but a part of the urethra remains open as a cleft at some point of the penis.

Epispadias is an opening of the urethra on the upper side of the penis. It presents various grades and forms.[2]

Hermaphroditism.—This is a union of two sexes in the same person, the test of which is the presence of the secreting organs, the ovaries and testicles. True hermaphroditism may perhaps occur, although most of the conditions called hermaphroditism are in reality due to varying malformations of the external generative organs.

Pseudohermaphroditism.—In the male, normally, the greater part of Müller's canal disappears and its lower end forms the vesicula prostatica. In this malformation Müller's canal is changed, as it is in the female, into Fallopian tubes, uterus, and vagina, while at the same times the testes, epididymides, vesiculæ seminales, and spermatic cord are formed as usual. In the lesser degrees of this malformation we find, in the place of the vesicula prostatica, a pear-shaped sac as large as a pigeon's egg, with muscular walls and an epithelial lining. This sac may be incompletely divided into a uterus and vagina, and open into the urethra. In the higher grades we find a well-formed vagina and uterus. The uterus may or may not have Fallopian tubes. The testicles are usually retained in the abdomen or inguinal canals, and are small. The spermatic ducts run on the sides of the uterus and open into the urethra or are closed. The penis and scrotum appear as in hypospadias, or are well formed. The appearance of the individual varies with the development of the testicles.

True Hermaphroditism.—There is considerable doubt as to the existence of true hermaphroditism, that is, in the sense that a person possesses separate and normally functionating male and female glands.[3]

[1] For a detailed consideration of the malformations of the male generative organs, consult *Klebs*, Handbuch d. pathologischen Anatomie, Berlin, 1873; *v. Neugebauer*, Hermaphroditismus beim Menschen, Leipzig, 1908; *Kermauner*, Schwalbe, Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, 1909, iii, 41; and *Sauerbeck*, Frankfurt. Ztschr. f. Path., 1909, iii, 339, 661, 829.

[2] For details of these malformations, see *Kaufmann*, Lehrbuch d. pathologischen Anatomie, 6th ed., Berlin, 1911, p. 900.

[3] For a discussion of the older classification, see *Kaufmann*, Lehrbuch d .spez. path. Anatomie, Berlin, 1911, ii, 904.

Enlargement of the penis is sometimes caused by venous congestion from heart disease; by long-continued masturbation, as a result of which the corpus cavernosum may lose its contractility; and in rare cases by hyperplasia of the stroma of the corpus cavernosum. Continuous erection is seen occasionally in myelogenous leukemia, and is probably due to thrombosis of the veins or of the sinuses. The phenomenon is met with, also, in infectious diseases and in metastatic tumors of the penis.[1]

INJURY AND HEMORRHAGE.

Injuries to the penis are liable to give rise to severe hemorrhage on account of its peculiar vascular character; suppurative inflammation, gangrene, infiltration with urine and its consequences, are also liable to occur. The contractions of the cicatricial tissue by which wounds are healed frequently give rise to various distortions of the organ.

INFLAMMATION.

Balanitis—inflammation of the glans penis and the prepuce—is usually due to gonococcal or syphilitic infection, or it may be incited by foul accumulations of smegma. The parts are red and swollen and may ulcerate. Condylomata may be formed, and adhesions between the prepuce and glans. The glans may ulcerate and the prepuce may be much thickened. If the prepuce be long, *phimosis* may occur with the accumulation of exudate beneath. The prepuce may become gangrenous.

Paraphimosis is produced by the retraction of a narrow prepuce behind the glans, with consequent stricture, inflammation, and sometimes gangrene.

Inflammation of the Corpora Cavernosa may be the result of injury, may follow fistulæ, may occur in connection with inflammation of the connective tissue of the penis, and may accompany the acute infectious diseases. It may result in fibrous induration of portions of the corpora cavernosa; rarely in abscess or diffuse purulent infiltration; sometimes in gangrene Larger and smaller masses or plates of very dense fibrous tissue sometimes form in the sheath of the corpora cavernosa without history of antecedent lesion.[2]

Tuberculous Inflammation of the penis has repeatedly followed ritualistic circumcision performed by persons suffering from pulmonary tuberculosis. The presence of acid-fast bacilli (*smegma bacilli*) in the sebaceous secretion of the preputial glands and in the urethra is a reason for great caution in diagnosing tuberculosis from the presence of bacilli alone.

Syphilitic Ulcers frequently occur in the glans penis and prepuce. The indurated chancre is derived either from an excoriation in which a pustule is formed or from a little nodule. The pustule breaks and its walls are infiltrated with small round cells. The nodule softens, breaks down, and forms an ulcer whose walls are infiltrated with cells,

[1] *Blum, V.*, Wien. klin. Wchnschr., 1906, xix, 1133; *Rosenthal, F.*, Berl. klin. Wchnschr., 1910, xlvii, 147.

[2] For a study, with bibl., of indurations in the corpora cavernosa penis, see *Sachs, M.*, Wien. klin. Wchnschr., 1901, xiv, 999.

and whose vessels have the characteristic perivascular lymphatic infiltrations. Syphilitic condylomata occur frequently on the glans.

Soft chancre may occur on the prepuce or glans, and is often accompanied by suppurative inflammation of the inguinal nodes (*bubo*). The streptobacillus of Ducrey may be demonstrated in the pus.

Herpes of the prepuce occurs in the form of small vesicles, which may later become ulcers. **Erysipelatous and furuncular inflammation** sometimes involves the skin of the penis.

TUMORS.

Papilloma is found on the prepuce and glans penis. It occurs in the form of little warty growths (*condylomata acuminata*), or of composite, cauliflower masses, even as large as a fist. In either case the structure is the same—hypertrophied papillæ covered with epithelium. Sometimes the epithelial layers become thick and horny, forming large, dense projections. Papillomata may become malignant and invade the glans and the inguinal nodes.

Fibroma diffusum, or elephantiasis of the prepuce, may occur, leading to great thickening. It is due to a diffuse growth of fibrous tissue in the cutis. **Lipoma, angioma, circumscribed fibroma,** and **sebaceous cysts** may occur in the penis. **Carcinoma,** which is most frequent in the prepuce and glans penis, is usually of the epitheliomatous type, and may have the form of a flat ulcer, or of infiltrating, ulcerating nodules, or may be papillary. Such growths may attain great size, ulcerate, or undergo a variety of inflammatory changes. Carcinoma may involve the entire skin of the penis or may invade deeper parts; the inguinal glands may be involved. Distant metastases are not frequent Medullary or glandular carcinoma of the penis is not common. It may be secondary to carcinoma in some other part of the body.[1]

Sarcoma of the vascular[2] and melanotic types[3] occurs in the penis.

Dermoid tumors of the penis are of occasional occurrence.[4]

Calcification and **ossification** of the connective tissue of the corpora cavernosa sometimes occur.[5] Large and small **preputial calculi** are occasionally found between the prepuce and the glans. These may be formed in situ, may come from the bladder or from without, and may later increase in size.

The Scrotum.

The skin of the scrotum is subject to the various types of lesions which may occur in any part of the integument.

Elephantiasis of the scrotum consists in the main of a development of new connective tissue in the cutis, which is sometimes accompanied by dilatation of the lymph-vessels; thus the thickened scrotum may form a

[1] *Küttner,* Beitr. z. klin. Chir. (Bruns), 1900, xxvi, 1.
[2] *Colmers, F.,* Zieglers Beitr., 1903, xxxiv, 295; *Borrmann, R.,* Lubarsch-Ostertag, Ergebn. d. allg. Path., 1900, vii, 833.
[3] *Payr,* Deutsch. Ztschr. f. Chir., 1899, liii, 221.
[4] *Gerulanos,* Deutsch. Ztschr. f. Chir., 1900, lv, 326.
[5] *zur Werth, M.,* and *Scheele, K.,* Deutsch. Ztschr. f. Chir., 1913, cxxi, 298.

large tumor, often rough upon the surface, which may entirely cover in the penis.

TUMORS.

Lipoma and **fibroma** occur. **Epitheliomata,** in the form of flat or papillary ulcerating tumors, are of frequent occurrence among chimney sweepers[1] and coal tar workers, and may lead to extensive ulcerations of the adjacent parts and involvement of neighboring lymph-nodes.

Dermoid Cysts and Teratomata of the scrotum are not uncommon. In very rare cases tumors containing a considerable portion of a fetal skeleton have been found in the scrotum. Occasionally the skin of the scrotum is beset with numerous larger and smaller sebaceous cysts, which raise the surface into little globular or wart-like projections.

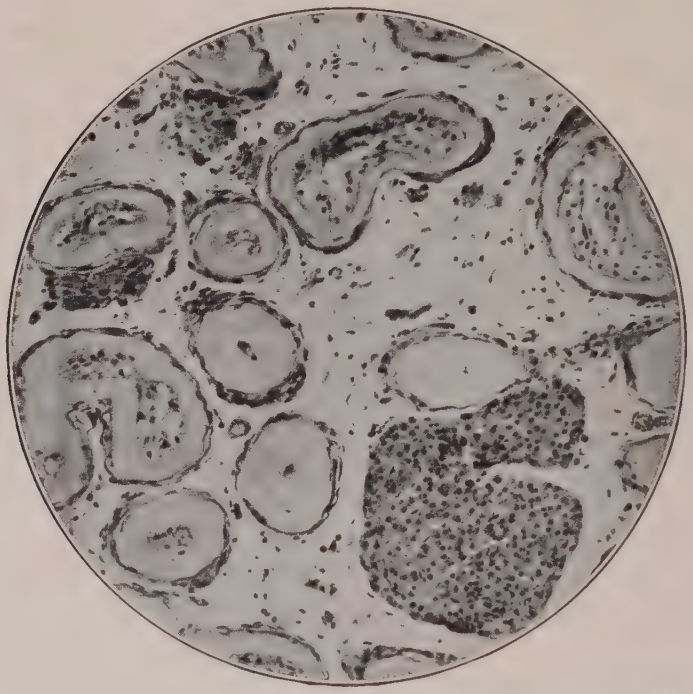


FIG. 710.—UNDESCENDED TESTICLE IN AN HERMAPHRODITE OF FEMALE TYPE. Showing atrophy of the tubules and retention of the interstitial cells.

The Testicles.

Malformations.

Absence of both testicles, either with or without absence of the epididymides, spermatic cords, and vesiculæ seminales, occurs in rare cases. The scrotum is only indicated or may contain the epididymides. The penis is small, and the individuals are small and poorly developed.

[1] *Butlin, H. T.*, Brit. Med. Jour., 1892, i, 1341; ii, 1; *Morley, J.*, Lancet, 1911, ii, 1545.

The testes may be imperfectly developed. The individuals are effeminate. Absence of one testicle with healthy development of the other, is more frequent. The corresponding epididymis and cord may be absent or present.

The spermatic cords and vesiculæ seminales may be absent or imperfectly developed on one or both sides, while the testes are normal.

Cryptorchismus.—Either one or both testicles may remain permanently in their fetal position, or may not descend into the scrotum for several years after birth (*cryptorchismus*), or not at all. This condition, which occurs in about two per thousand of healthy males, may be due to an arrest of development in the testes or the gubernaculum testis; adhesions produced by antenatal peritonitis; narrowing of the inguinal canal; narrowing or shortening of the vaginal process of the peritoneum; or to abnormal size or position of the testicle. Usually the malformation is confined to one testicle, and then is more frequent on the left side. The testicle is usually found in the abdomen close to the mouth of the inguinal canal, or in the inguinal canal just below the external ring; but it may be beneath the skin in the perineum, or in the crural canal with the femoral vessels, or elsewhere. Hernia is present in half the cases. The retained testis is usually not fully developed, or undergoes fatty degeneration or fibrous hyperplasia. The interstitial cells are often increased, and may even form macroscopic nodules (Fig. 710).[1] The retention of one or even of both testicles does not preclude the possibility of procreation. Retained testicles are prone to inflammatory changes; they early lose the capacity to furnish spermatozoa, and are liable to become the seat of malignant tumors.[2]

Sometimes, while the testis is retained, the epididymis and spermatic cord descend into the scrotum. In rare cases the position of the testis may be changed so that the epididymis and cord are in front. The occurrence of supernumerary testicles is described.

Fig. 711.—Varicocele.
The distended and tortuous vessels have been filled with wax.

Varicocele.

In varicocele the veins of the spermatic cord are dilated, often forming tortuous masses of considerable size (Fig. 711).

Hydrocele.

In *hydrocele* of the *tunica vaginalis* there is an accumulation of fluid in the cavity of the sac. It is usually unilateral and is commonly associated with acute or chronic inflammation of the tunica vaginalis, varicocele, or general dropsy. The serum is present in small or in large quantity; it is usually transparent, may contain cholesterin, or be purulent or mixed with blood. The tunica vaginalis remains unchanged, or is thickened, or contains plates of bone, or is covered with polypoid fibrous bodies which may fall off and be found

[1] *Odiorne* and *Simmons*, Ann. Surg., 1904, xi, 962.

[2] For histology of undescended testicle, see *Uffreduzzi*, Arch. f. klin. Chir. (Langenbeck), 1913, c, 1151; and ci, 150. For a study of malignant tumors of the undescended testicle, see *Bulkley*, Surg., Gynec., and Obst., 1913, xvii, 703 (bibl.); see also, *Butt*, ibid., 1914, xix, 419.

free in the cavity of the sac. There may be adhesions between the layers of the tunica vaginalis, and in this way the fluid becomes sacculated. The testis is pushed downward and backward; it remains unchanged or is atrophied.

In *hydrocele of the processus vaginalis* there is an accumulation of serum in the cavity of the vaginal process of the peritoneum, which remains open after the descent of the testicle. There are several varieties.

(*a*) The vaginal process is entirely open and there is a free communication with the peritoneal cavity. The serum may originate in the cavity of the peritoneum or of the vaginal process, and passes freely from one to the other.

(*b*) The processus vaginalis is closed in the inguinal canal, while its lower portion is filled with serum.

(*c*) The processus vaginalis is closed about the testis and the visceral layer of the tunica vaginalis is formed. The serum accumulates in the upper part of the vaginal process which communicates with the peritoneal cavity.

(*d*) The vaginal process is closed in the inguinal canal and over the testis; the serum accumulates so as to form one or more sacs between these two points. Inguinal hernia may complicate this form of hydrocele.

In *hydrocele of the spermatic cord* there is general edema or the development of circumscribed cysts in the connective tissue of the cord.

A peculiar type of hydrocele is formed by the accumulation of serum in the sac of an inguinal hernia from which the intestine has become retracted.

Hematocele.

In hematocele of the tunica vaginalis there is an effusion of blood into the cavity of this sac. It may occur in injury, in scurvy, or with the hemorrhagic diathesis, or it may complicate a pre-existing hydrocele. The effused blood usually soon degenerates, and the sac is filled with a brownish fluid or a thick, grumous mass. The tunica vaginalis may be thickened. The testis may remain normal or be atrophied.

Effusion of blood into the loose connective tissue of the scrotum is often called *extravaginal hematocele.*

Hematocele of the spermatic cord occurs in rare cases as a diffuse infiltration of blood in the connective tissue of the cord; or blood may be effused into a hydrocele of the cord.

Spermatocele.

Cysts containing spermatic fluid not infrequently arise from the epididymis or from the rete testis. These sometimes acquire a large size and crowd the tunica vaginalis before them, so that they simulate a collection of fluid in the cavity of the latter. The wall of the cyst may be lined with ciliated or with flattened epithelium. The contents are sometimes simply serous, but more frequently opalescent, and may contain spermatozoa.[1]

ATROPHY.

Atrophy of the testicle may occur in old age or in persons who are in a condition of premature senility; or as the result of injury or of pressure from herniæ, hydrocele, or inflammatory products. Fatty degeneration and the accumulation of various degeneration products in the lumen of the tubules may accompany atrophy.

INFLAMMATION. (Orchitis.)

Inflammation of the testicles may follow injuries, exposure to cold, and gonorrheal inflammation of the urethra; it may occur in parotitis or

[1] *Hanusa*, Beitr. z. klin. Chir. (Bruns), 1910, lxix, 255; *Whitney, C. M.*, Am. Jour. Urol., 1907, iii, 175 (bibl.).

with syphilis and various other infectious diseases, among which may be mentioned scarlet fever, typhoid fever, cerebrospinal fever, pneumonia, and variola. The testes, epididymis, or tunica albuginea may be principally involved. Usually only one testicle is inflamed, sometimes both. The inflammation may extend to the vas deferens.

Acute Exudative Orchitis is most frequent in the epididymis and tunica albuginea. When the testis is involved the organ is congested and infiltrated with serum or pus. From this condition it may return to the normal state; or small abscesses may form which may be absorbed, or increase in size so as to involve nearly the entire organ. They may perforate externally, and then healing may occur by means of granulation tissue; or extensive gangrenous destruction of the scrotum may occur. Abscesses may become inclosed in a fibrous capsule, when the

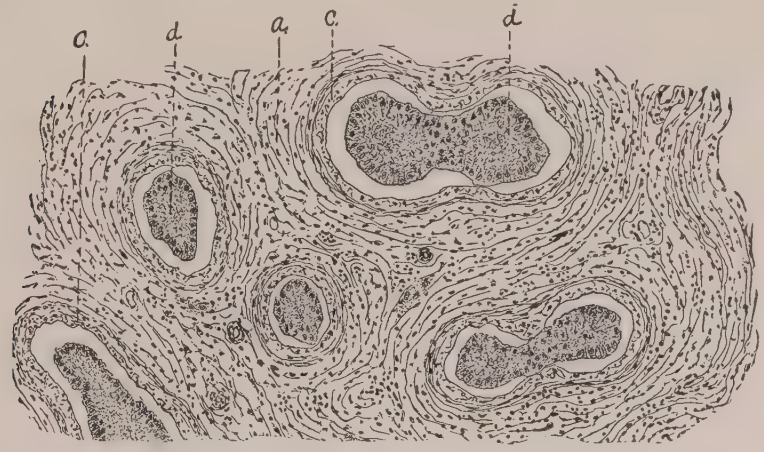


FIG. 712.—CHRONIC INTERSTITIAL ORCHITIS WITH ATROPHY OF THE SEMINIFEROUS TUBULES. *a*, Thickened interstitial tissue; *c*, thickened membrana propria of the tubules; *d*, separated epithelial cell mass in the lumina of the tubules.

contents may dry and become caseous or calcified, and so persist for a long time. The acute inflammation may become chronic.

Acute epididymitis is frequently the result of gonorrheal infection, and may or may not be associated with inflammation of the testis. The products of inflammation may collect in varying quantity in the lumina of the seminiferous tubules and in the ducts of the epididymis, and the epithelium of these structures may degenerate. As the inflammation subsides, the contraction of the connective tissue may obliterate the canals, which then become cystic. This type of epididymitis is, therefore, a frequent cause of sterility.

Chronic Orchitis, in some grade, is a frequent disease, being found in about 30 per cent. of adult males. The condition is due usually to an infectious process, and either is a consequence of an acute lesion or is chronic from the outset. Syphilis is responsible for about half of the cases, gonorrhea for a tenth; the proportion due to epidemic parotitis is

difficult to estimate. The other most frequent causes of the lesion are: tuberculosis, variola, leprosy, arteriosclerosis, indirect injury from the pressure of herniæ or hydrocele, and trauma. Undescended testicles, also, show a compensatory interstitial fibrosis due to the tubular atrophy.

The most striking feature of the lesion is the presence of more or less connective tissue in the organ; hence, the designation of the condition as *fibrosis testis*, a term to be preferred to chronic orchitis as the presence of inflammatory processes can not always be demonstrated.[1] The degree of the fibrosis found is very variable. In the less extensive lesions the only thing noticeable may be that the tubules do not well up from the cut surface of the organ as they do normally under these circumstances. After chronic inflammation the cut surface remains smooth, the tubules being held in their position by the new fibrous tissue. In the more extensive cases, there may be radiating bands of connective tissue extending throughout the organ, or the fibrosis may be limited to a particular portion. This is the usual form in arteriosclerosis, the fibrosis being limited to the periphery of the organ, and the atrophy of the tubules being evident from scattered pale transparent areas distributed irregularly, while the rest of the parenchyma is normal. In the most severe grades the whole organ is converted into a dense fibrous tissue mass, in which little or no glandular tissue can be recognized. The microscopic picture is equally variable. The increase in the connective tissue may be slight, and the disease may affect simply the seminal tubules, which are atrophic with thickened hyaline walls (Fig. 712). The epithelium is desquamated, and the lumen is filled with granular and hyaline masses of débris. The elastic tissue of the tubules remains fairly intact for a long period when there is no formation of granulation tissue.[2] The specific interstitial cells of the testicle are occasionally more abundant than normal.

In another type, the intercanalicular tissue may be greatly increased so that the seminiferous tubules are separated from each other by wide spaces. A considerable number of lymphocytes and plasma cells lie in the connective tissue, especially in the luetic cases; the lumina of the ducts are obliterated; the walls are thickened; the epithelium is desquamated; and only the elastic tissue remains. The albuginea in these instances is usually thickened. When the lesion is still more extensive, no remnants of the seminiferous tubules can be found, except a few fragmented elastic tissue fibers, and the whole testicle is converted into a solid fibrous tissue containing but few nuclei. Exceptionally, the tubular epithelium may proliferate and form solid areas which may lead to an erroneous diagnosis of neoplasm; the presence of remains of the interstitial cells has led to the same error. Calcification may take place in the newly formed connective tissue. When the lesion is advanced, there is often a periorchitis which leads to thickening and fusion of the layers of the tunica vaginalis. In the gonorrheal cases the fibrosis involves the epididymis, also, while in chronic syphilitic processes without

[1] *Simmonds, M.*, Virchows Arch., 1910, cci, 108.
[2] *Federmann, A.*, Virchows Arch., 1901, clxv, 469.

gumma formation the epididymis is free from extensive lesions. If a few of the tubules escape the injury, spermatozoa may be formed, and if the epididymis is not diseased the patient may not be sterile.

Tuberculous Orchitis may occur in connection with tuberculosis of the other genitourinary organs or of the lungs, in acute general miliary tuberculosis, or independently. It usually originates in the epididymis, and may extend from there to the testis; or it may commence in the testis. The appearance which the testicles present when they are the seat of this form of inflammation is exceedingly varied and often difficult of interpretation. This is partly due to the complex structure of the organ, partly to the varied complicating simple inflammatory changes which the different parts of the organ undergo in connection with the tuberculous lesion.

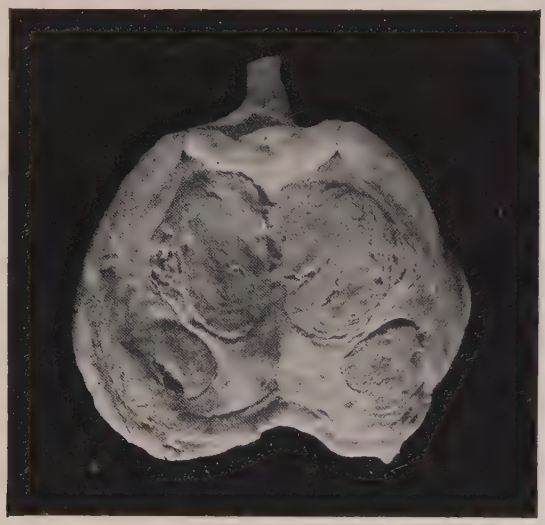


Fig. 713.—Tuberculous Orchitis.

We may find in the testicle small circumscribed masses of cells, visible to the naked eye as whitish spots, which are sometimes composed of small spheroidal cells or of larger polyhedral or fusiform or round cells. These occur in the walls of seminiferous tubules and blood-vessels, and in the interstitial tissue. Sometimes associated with these smaller nodules, and sometimes not, we find larger, irregular, yellowish or gray cheesy masses, which may be formed by the confluence and degeneration of the smaller nodules (Fig. 713). The cheesy masses may break down and open externally, giving rise to fistulæ, gangrenous inflammation, etc.

Coincident with this distinctly tuberculous nodular formation of tissue, which is disposed to degenerative changes, there are various more or less diffuse alterations of the parenchyma and interstitial tissue of the organ which often constitute a most prominent feature of the lesion. The interstitial tissue may be more or less densely and diffusely infil-

trated with small spheroidal cells. The arteries are often the seat of obliterating endarteritis. The walls of the seminiferous tubules may be very much thickened, so that the lumen may be entirely obliterated. The epithelium lining the tubules may be fatty, disintegrated, and peeled off, or it may have largely disappeared. The lumen of the tubules may be filled with a granular, nucleated mass which in transverse sections looks like a giant cell. The thickened walls of the tubules may be infiltrated with small spheroidal cells, so that the underlying stroma is scarcely visible. When this occurs in connection with a similar infiltration of the interstitial tissue and the formation of giant cells in the lumina, we have structures which present the greatest resemblance to some forms of tubercle granula (Fig. 714), though not tuberculous in nature.

Tuberculous inflammation may extend from the testis to the vas deferens, vesiculæ seminales, and prostate.

Syphilitic Orchitis.—This may occur in the form of a diffuse new formation of connective tissue, which may be localized or be widely dis-

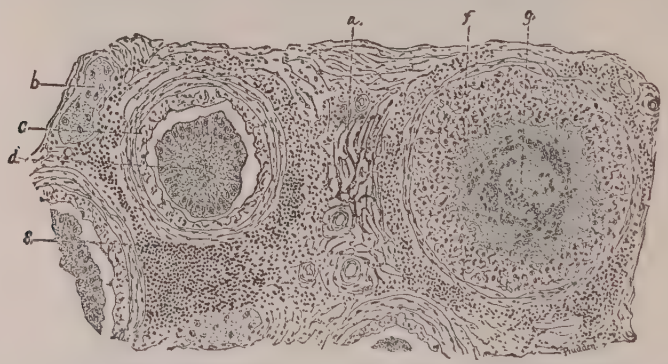


FIG. 714.—CHRONIC ORCHITIS WITH THE FORMATION OF STRUCTURES RESEMBLING MILIARY TUBERCLES.

a, Thickened interstitial tissue; *b*, mass of granular cells in the interstitial tissue; *c*, thickened membrana propria of seminiferous tubule; *d*, mass of separated epithelium in tubule; *e*, accumulation of small spheroidal cells around tubules; *f*, thickened membrana propria enclosing *g*, a multinuclear mass resembling a giant cell.

tributed. The organ becomes dense and firm. Morphologically there is no constant difference between this form of orchitis and chronic indurative orchitis from other excitants; but occasionally the perivascular lymphocytic infiltration may give a clue to the origin. It may occur in children affected with congenital syphilis. Gummata may form in connection with the interstitial induration. These may disappear, leaving irregular cicatrices, yet have but little tendency to soften and break down as do the tuberculous lesions.

The differential diagnosis between tuberculous and syphilitic orchitis is difficult.[1] The vascular changes, the better preservation of the elastic fibers in gummata, and the infrequence of giant cells and well formed tubercles, may permit of a decision. The fact that testicular gummata do not soften so frequently as tubercles may assist in the differentiation. A

[1] For a discussion of the histological differentiation between tuberculous and syphilitic orchitis, see *Baumgarten*, Verhandl. d. deutsch. path. Gesellsch., 1901, iii, 107.

positive Wassermann reaction points toward gumma, but does not exclude tuberculosis.

In **leprosy,** inflammatory foci in the testicle are common, leading ultimately to a fibrosis.[1]

Actinomycosis and **glanders** may rarely affect the testicle.

TUMORS.

There is scarcely an organ whose tumors have given rise to more discussion—partly because no one observer has had any wide experience, since new growths are not especially frequent in this organ,[2] and partly because neoplasms at one time regarded as independent have come to be interpreted as predominating constituents of mixed tumors.[3] Thus, a careful examination of such growths as adenoma, "carcinoma," sarcoma, chondroma, lipoma, myxoma, etc., has demonstrated in many cases the

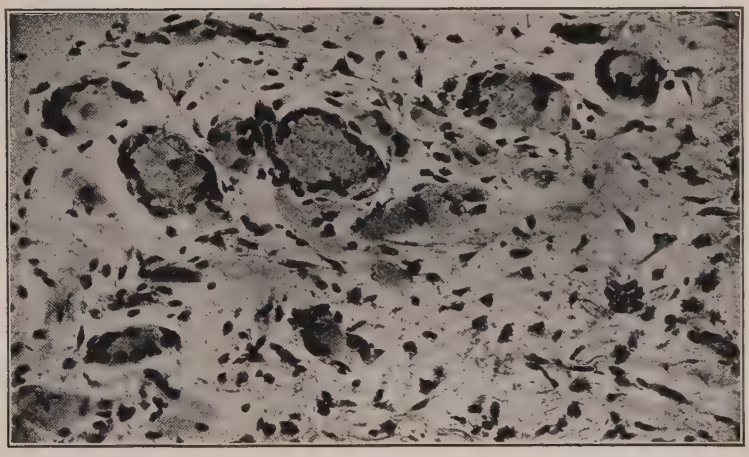


FIG. 715.—RHABDOMYOMA OF THE TESTICLE.
Imperfect striated muscle fibers lie in an embryonal connective tissue.

presence of derivatives of all three germinal layers. A pure **fibroma** may possibly occur, though it is extremely rare, as is pure **chondroma; myxoma** and **lipoma** probably do not arise apart from mixed tumors. **Myomata** have been observed, not, however, of strictly testicular origin, having sprung probably from the vas deferens, the walls of the epididymal canals,[4] or the cremaster muscle (*leiomyoma*), or from the gubernaculum testis (*rhabdomyoma*, Fig. 715).[5] They may represent, also, a portion of a mixed tumor.

[1] For a summary of leprous orchitis, consult *Sébileau*, Arch. gén. de méd., 1899, i, 636, 757 (bibl.).

[2] Tumors are said to be somewhat more common in undescended testicles than in the normal gland. For bibl., see *Bulkley*, Surg., Gynec., and Obst., 1913, xvii, 703. For a general discussion of tumors of the testis, see *Miyata*, Arch. klin. Chir. (Langenbeck), 1913, ci, 426 (bibl.).

[3] For a discussion of the question, see *Ewing*, Surg., Gynec., and Obst., 1911, xii, 230 (bibl.); and *Debernardi*, Zieglers Beitr., 1907, xl, 534 (bibl.).

[4] For cancer and other tumors of the epididymis, see *Sakaguchi*, Frankfurt. Ztschr. f. Path., 1914, xv, 62 (bibl.).

[5] *Becker*, Virchows Arch., 1901, clxiii, 244 (bibl.).

Adenoma sometimes develops as part of a teratoma, but very rarely as an independent neoplasm.[1]

The question of **sarcoma** is unsettled, the nature of the growths described as *small round-cell* or *spindle-cell* sarcoma being still undetermined. The former, most familiar of the new growths of the testis, is called also *lymphadenoma* and *lymphosarcoma.*

Carcinoma is in a similarly doubtful position. Strictly speaking there is, of course, no such thing as carcinoma of the testis, since this gland is of mesodermal origin.

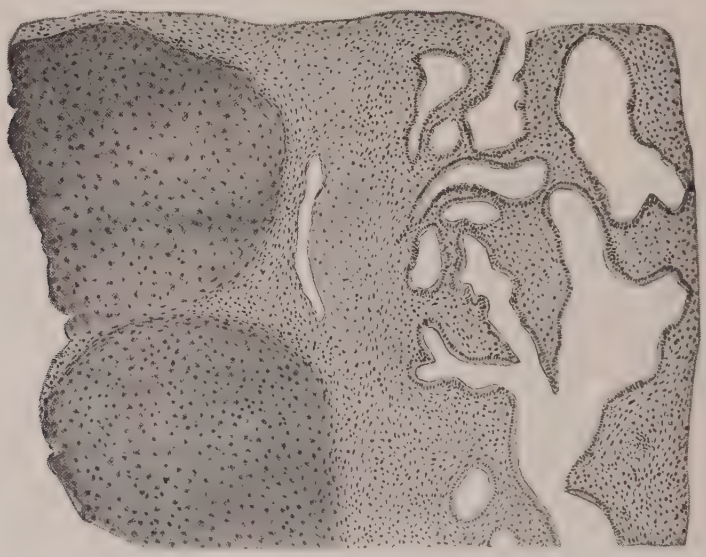


FIG. 716.—TERATOMA OF THE TESTICLE.
Masses of hyaline cartilage at the left; new-formed atypical glandular structures at the right.

A tumor[2] called by many observers simply **large round-cell tumor** of the testis, in the absence of any definite information as to its actual character, is regarded by some pathologists as an independent *carcinoma*, by another group as a *sarcoma*, by others as a derivative of the spermatoblast (*seminoma*)[3] or of the interstitial cells of Leydig, and by still others as merely the predominating constituent of a teratoma.

The type which is said to originate in the interstitial[4] cells of the testis, though this derivation is not by any means universally accepted, is a firm, rapidly growing neoplasm which may metastasize. It is composed of interlacing strands of large cells looking somewhat like epithelium; these groups are interrupted by an acellular stroma but there is

[1] *Pick*, Berl. klin. Wchnschr., 1905, xlii, 502 (bibl.); *Kaufmann*, Deutsch. med. Wchnschr., 1908, xxxiv, 803.

[2] *Debernardi*, Zieglers Beitr., 1907, xl, 534 (bibl.); *Franke, A.*, Frankfurt. Ztschr. f. Path., 1912, ix, 206 (bibl.).

[3] *Chevassu*, Tumeurs du testicule, Thèse de Paris, 1906.

[4] *Kaufmann*, Verhandl. d. deutsch. path. Gesellsch., 1907, xi, 237 (bibl.); Deutsch. med. Wchnschr., 1908, xxxiv, 803 (bibl.); *Stoppato*, Zieglers Beitr., 1911, l, 113 (bibl.).

no definite alveolar arrangement. The cells resemble the normal interstitial elements. The cytoplasm may be abundant like that of the liver cell, or smaller in amount and vacuolated. The nuclei are of moderate size (8 to 16 micra), vesicular, round, often eccentrically placed, and provided with one or two nucleoli.

Teratoma.[1]—These neoplasms are described in the older text-books under the name *cystoma* or *adenoma*, but are now suspected by many to arise from dissociated blastomeres.[2] A blastomere is one of the cells resulting from the first few divisions of the fertilized ovum. The earliest are totipotent, since any of them can produce all the tissues of the body.

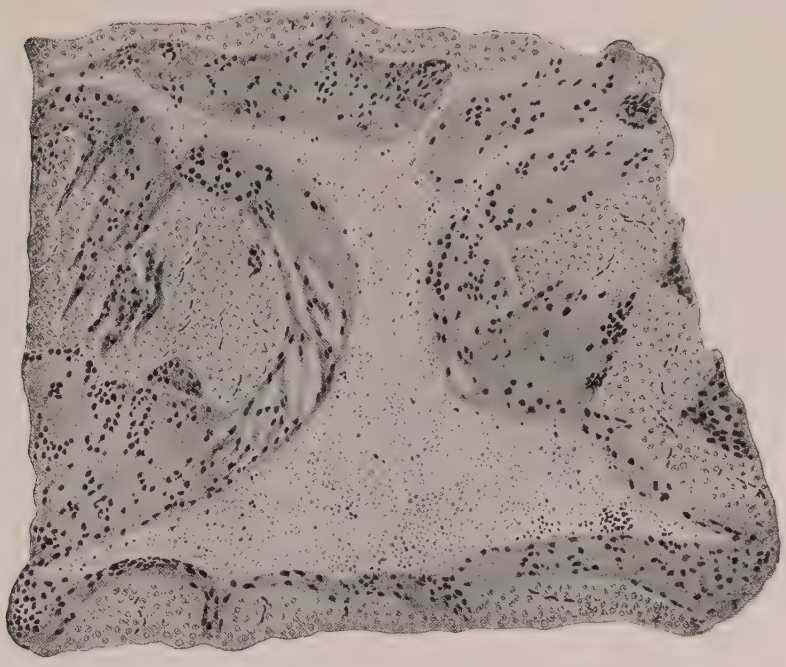


FIG. 717.—CHORIONEPITHELIOMA OF THE TESTICLE.
Showing syncytium and Langhans' cells and their relation to blood sinuses.

Hence, they differ from their descendants, which become gradually multipotent, or able to evolve many tissues though not all, and finally unipotent, or capable of building but one.

Teratomata of the testis are believed to arise at a time when the blastomere is totipotent, and these growths are, therefore, potentially tridermal, *i.e.*, may contain derivatives of all three germinal layers (Fig. 716). But one constituent may grow so vigorously as to overshadow

[1] *Meyer, Rudolf*, Frankfurt. Ztschr. f. Path., 1913, xiii, 215 (bibl.).

[2] *Marchand*, article Missbildungen, in Eulenberg's Real Encyclopädie der gesammten Heilkunde, 3d ed., Vienna, 1897, Bd. xv, p. 506; *Bonnet*, Monatschr. f. Geburtsh. u. Gynäk., 1901, xiii, 149; *Wilms*, Zeiglers Beitr., 1896, xix, 233; Deutsch. Ztschr. f. klin. Chir., 1898, xlix, 1; Die Mischgeschwülste, Leipzig, 1899–1902.

or even suppress the others, so that the presence of one tissue only is not proof positive against a teratomatous origin.

Not all pathologists accept the foregoing explanation. Thus it has been asked[1] why teratomata occur almost always in the testis or ovary if they originate from the blastomeres in general, and it has been suggested that in the testis and ovary they arise from among those blastomeres which eventually go to form these two organs.

Now, since derivatives of all three layers are potentially present in a teratoma of the testis, the tumor, like a normal embryo, will tend to develop a chorion. Thus is explained the **chorionepithelioma** (Fig. 717) of the testis,[2] a malignant and rapidly metastasizing neoplasm similar to that found in the female.

PARASITES.

Echinococcus may occur in the testis or epididymis.

The Seminal Vesicles.

The seminal vesicles may be the seat of **acute or chronic inflammation,** which is most frequently associated with inflammatory changes in adjacent parts, prostate, urethra, etc. As a result of chronic inflammation the vesicles may be atrophied, or they may be greatly dilated, forming cysts due to constriction of the ducts. **Tuberculous inflammation** is usually secondary.[3]

TUMORS.

Carcinoma of the rectum or other genitourinary organs may secondarily involve the seminal vesicles. Primary tumors are very infrequent. Small **concretions,** sometimes containing masses of spermatozoa, are occasionally found in the seminal vesicles. **Rhabdomyomata** have been found in the seminal ducts.[4]

The Prostate.

DEGENERATION, ATROPHY, AND HYPERTROPHY.

Fatty and **hyaline degeneration** of the epithelium and the muscle cells may occur in the prostate with or without hypertrophy. A moderate amount of brown pigment is often found in the muscle fibers and in the connective tissue about the gland in old age.

Atrophy of the prostate may follow acute lesions, orchitis, orchidectomy, and ligature of the vas deferens, or may occur as a senile process. Usually the atrophy following orchidectomy and ligature of the vas is

[1] *Ribbert*, Die Geschwulstlehre, 2d ed., Bonn, 1914, p. 674; *Adami*, Principles of Pathology, Philadelphia, 1st ed., 1908, i, 605.

[2] *Schlagenhaufer*, Wien. klin. Wchnschr., 1902, xv, 571; *Franx, R. T.*, Jour. Am. Med. Assn., 1906, xlvi, 256 (bibl.); *Risel*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1907, xi[2], 928; *Cooke*, Bull. Johns Hopkins Hosp., 1915, xxvi, 215 (bibl.); *Woglom*, St. Luke's Hospital Medical and Surgical Reports, vol. iv, New York, 1917, p. 188 (bibl.).

[3] *Walker, G.*, Johns Hopkins Hosp. Rep., 1911, xvi, 1.

[4] *Mönckeberg*, Virchows Arch., 1907, clxxxvii, 471.

slight, and any improvement which occurs is due to reduction of the congestion of the gland and mucous membrane over it, rather than to a great reduction in the amount of connective tissue.

Hypertrophy.[1]—Enlargement of the prostate—so-called hypertrophy—is of fairly frequent occurrence in old age; but occasionally it is seen before forty. It is rather more frequent among the better classes. The organ may be very greatly enlarged (Fig. 718), and may project forward into the bladder, or chiefly toward the rectum. The middle lobe of the gland is the one most frequently attacked and the one which causes the physical symptoms which call attention to the lesion by pressure upon

FIG. 718.—HYPERTROPHY OF THE PROSTATE.

the urethra, thus rendering urination difficult or impossible. Such partial or complete closure is regularly associated with other conditions, such as hypertrophy and dilatation of the bladder, trabeculation of the walls, or even the formation of diverticula. Dilatation of the ureter and hydronephrosis also may follow prostatic hypertrophy. If infection takes place cystitis, pyelitis, or suppurative pyelonephrosis may occur.

Microscopical examination of the enlarged prostate shows a considerable variety of pictures. The glandular hyperplasia may be extreme (Fig. 719), and the gland may be converted into what is practically a multilocular cyst. On the other hand, the fibro-muscular tissue may undergo a very great hyperplasia without marked increase in the glands. This hyperplasia may be diffuse or nodular, and this is equally true of

[1] For a discussion of pathological changes in the prostate, see *Wilson, L. V.*, and *McGrath, B. F.* Surg., Gynec., and Obst., 1911, xiii, 647.

the hyperplasia of the glandular tissue. Corpora amylacea are regularly present, though not in as large numbers as in the normal prostate (Fig. 723). The interstitial tissue especially about the gland is usually infiltrated with lymphocytes, and occasionally this infiltration is quite diffuse. When the hypertrophy of the gland is circumscribed, nodules of muscle and fibrous gland tissue which are formed near the periphery of the organ may project into the bladder and even become detached and be found as small movable tumors beneath the mucous membrane.

This variation in the composition of the enlarged prostate leads to the different clinical types—the small hard enlargement, the nodular type, and the diffuse spongy vascular form

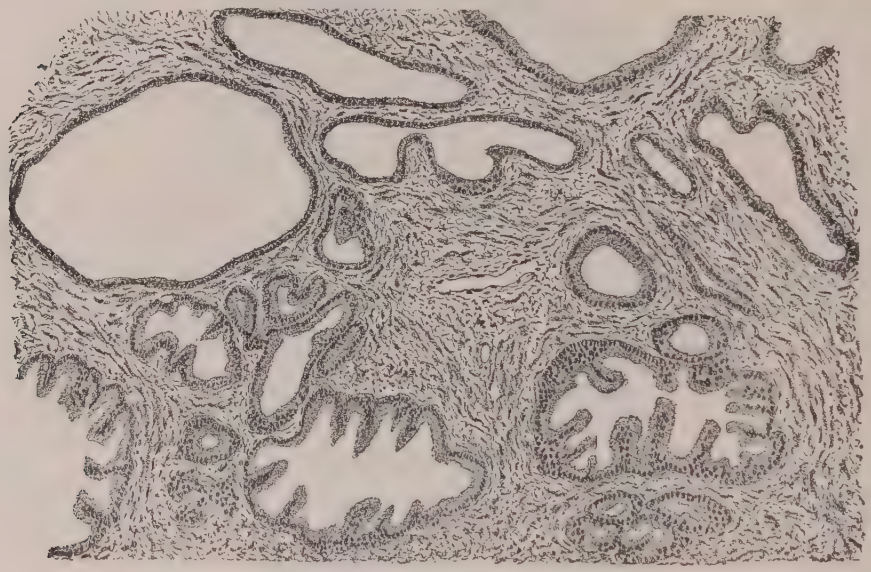


FIG. 719.—"HYPERTROPHY"—HYPERPLASIA—OF THE PROSTATE.
There is a glandular hyperplasia as well as hyperplasia of the fibromuscular stroma.

In consequence of the enlargement of the gland the deep urethra is pushed up and, hence, is longer than normal; this lengthening may be increased by the formation across the urethral opening of a valve formed of prostatic tissue.

The cause of prostatic hypertrophy is still unknown. It has been considered as a consequence of a productive inflammatory lesion of the connective tissue.[1] This inflammatory thickening of the connective tissue leads to retention of the secretion and ultimately to a distention of the peripheral portion of the glandular structures. Others believe that the hypertrophy should be regarded as a tumor-like adenomatous growth,[2] and point to the extreme frequency with which carcinoma occurs, in

[1] *Ciechanowski*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1900, vii, 183.
[2] *Ribbert*, Zieglers Beitr., 1915, lxi, 149.

some series as high as 20 per cent.,[1] though 10 per cent. is nearer the average. Still others have called attention to the analogous position occupied by the uterus and the prostate and have suggested that the hypertrophy was similar in nature to the myomata of the uterus. Even the rather far-fetched analogy with chronic cystic mastitis of the female breast has been cited as possibly pointing to the fact that the hypertrophy of the prostate represents a senile involutionary change.

The recurrence of prostatic enlargement has been noted after removal of part of the gland, though without any evidence of tumor formation.[2]

INFLAMMATION. (Prostatitis.)

Acute exudative inflammation of the prostate may be induced by urethral gonorrhea, metastatic infection from other foci in the body, or

FIG. 720.—RHABDOMYOSARCOMA OF PROSTATE GLAND.
Showing area with abundant muscle fibers of embryonic type; striations only occasionally visible.

extension of infections of the seminal vesicles and rectum. The acute process may become chronic without abscess formation, or large quantities of pus may collect in the organ which can then be palpated as a swelling through the anterior rectal wall. These large abscesses may perforate into the rectum or into the urethra, and thus undergo spontaneous cure. Smaller abscesses usually perforate into the urethra. On the other hand, the inflammation may extend to the capsule of the prostate and set up an extensive prostatic inflammation, often with most serious consequences.

Tuberculous inflammation of the prostate may be confined to that organ,[3] but usually accompanies a similar lesion of some of the other

[1] *Judd, E. S.*, Surg., Gynec., and Obst., 1915, xx, 274; and *MacGowan*, Jour. Am. Med. Assn., 1917, lxviii, 521.
[2] *Paul, T.*, Lancet, 1910, ii, 294.
[3] *Koch, G.*, Frankfurt. Ztschr. f. Path., 1907, i, 272.

genitourinary organs.[1] Large cheesy masses are often formed, which may break down and open into the bladder or rectum.

TUMORS.[2]

Sarcoma of the prostate is very rare;[3] a few cases of **rhabdomyosarcoma** have been reported (Fig. 720).[4] **Adenoma**[5] (Fig. 721) occurs either

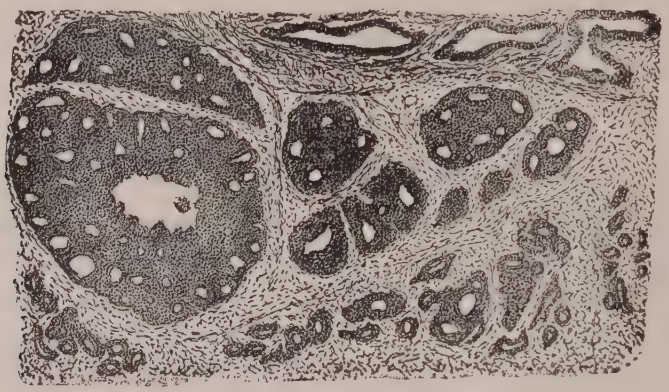


FIG. 721.—ADENOMA OF THE PROSTATE.

In the upper portion of the cut, at the right, are three nearly normal acini of the prostate, while the remainder shows various phases of new gland formation. The prostate, in addition to the circumscribed tumor growth, was the seat of the usual glandular and interstitial hyperplasia.

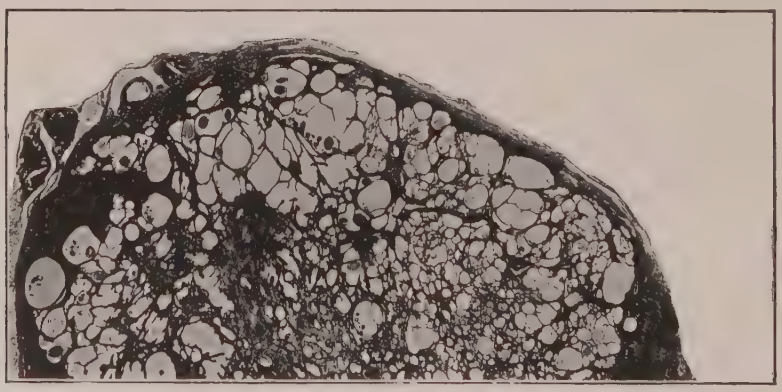


FIG. 722.—GLANDULAR HYPERPLASIA OF THE PROSTATE WITH CYSTIC DILATATION.
Some of the dilated glands contain corpora amylacea.

with or without an increase in the fibromuscular interstitial tissue and gland hyperplasia.

[1] *Halle, N.*, and *Motz, B.*, Ann. d. mal. d. org. génito-urin., 1903, xxi, 481, 561.

[2] For bibl. of prostatic tumors, see *McGrath, B. F.*, Jour. Am. Med. Assn., 1914, lxiii, 1012; also *Socin-Burckhardt*, Deutsch. Chirurgie, Lief 53, 1902, which has a very complete list of references to papers on prostatic disease.

[3] *Veil, W.*, Berl. klin. Wchnschr., 1908, xlv, 872, 924; *Cumston, C. G.*, Internat. Abs. Surg., 1914, xviii, 417.

[4] *Squier, J. B.*, Surg., Gynec., and Obst., 1916, xxiii, 341.

[5] *Ribbert*, Zieglers Beitr., 1915, lxi, 149.

Carcinoma is of frequent occurrence in hypertrophied prostates, involving as high as 10 to 20 per cent. of carefully examined specimens in certain series.[1] Such tumors are especially apt to form bone metastases. Secondary carcinoma is usually due to extension from the rectum.

Cysts of the prostate (Fig. 722) are sometimes formed either as a result of occlusion of the ducts by hypertrophy of the interstitial tissue, by tumors, etc., or as a result of faulty development.[2]

PARASITES AND CONCRETIONS.

Echinococcus of the prostate has been described, but is rare.

Concretions.—Small ovoidal or spheroidal, often brown or black bodies, having the characters of corpora amylacea (Fig. 723), are of very

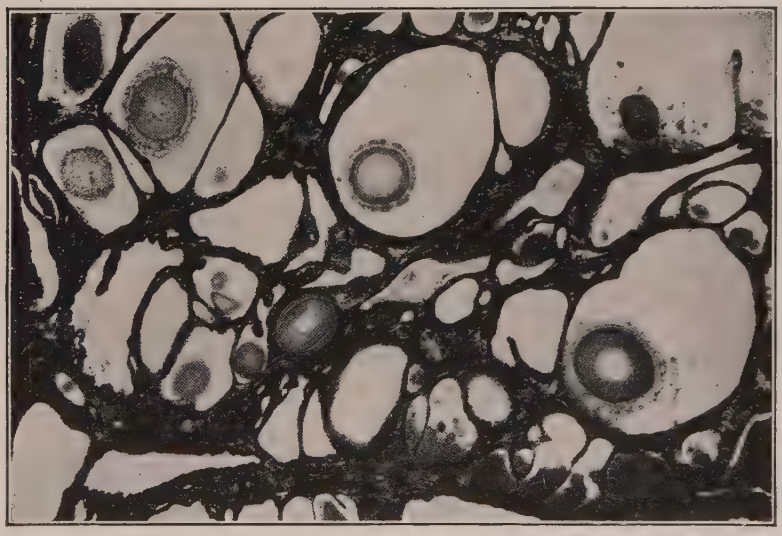


Fig. 723.—Corpora Amylacea in Glandular Hyperplasia of the Prostate.

frequent occurrence in the alveoli of the prostate, particularly in old persons. We find a certain number of them in the prostates of nearly all old men, but they are sometimes present in great numbers. Larger, irregular concretions, apparently formed by the coalescence or growth of the smaller ones, are less frequently found, and may be encrusted with lime salts. These concretions may give rise to ulceration of the ducts of the gland or to interference with the passage of urine, but usually they are of no practical importance.

Cowper's Glands.

Inflammatory processes, acute or chronic, may occur in these organs in connection with urethritis or prostatitis. Abscesses may form; the

[1] *Judd, E. S.*, Surg., Gynec., and Obst., 1915, xx, 274; *Gunn, L. G.*, Amer. Jour. Urol., 1915, xi, 243.

[2] The occurrence of squamous epithelium in the ducts and sinuses of the prostate has been described; see *Schmidt*, Zieglers Beitr., 1906, xl, 120.

glands, either in acute or chronic inflammation, may become enlarged and encroach upon the lumen of the urethra. *Retention cysts* formed by the closure of the excretory ducts may also project into the urethral canal.

The Male Mamma.

There may be an abnormal number of mammæ. In boys, at about the time of puberty, the mammæ may be swollen and inflamed or they may secrete milk. Cases are recorded in which adult males possessed large mammæ which secreted milk. The breasts may be enlarged from an increase of fat or of connective tissue.

Fibroma, fibroadenoma, cystadenoma,[1] **sarcoma, cystosarcoma, myxoma,** and various forms of **carcinoma**[2] may occur.

Cysts of the male breast are not very infrequent.

[1] *Unger*, Virchows Arch., 1901, clxv, 550.

[2] For bibliography of carcinoma of the male breast, see *Warfield*, Bull. Johns Hopkins Hosp., 1901, xii, 305.

CHAPTER XII.

VOLUNTARY MUSCLE.

ANATOMY.

In the embryo, muscle fibers begin as round or oval cells with single nuclei. As development goes on, these cells elongate, and become oval or club shaped and the nuclei multiply, occupying a central clear area; while the cytoplasm quickly differentiates into fibrils bearing transverse striations. The fibrils are arranged in small groups which show on cross-section as polyhedral areas—*Cohnheim's fields.*[1] The protoplasm is granular, and some of these granules give an oxidase reaction,[2] and under normal conditions contain glycogen. The muscle fibers are inclosed in a sarcolemma which is a clear, transparent, fibrous sheath, much tougher than the muscle fibers themselves, as they can be ruptured while the sarcolemma remains still inclosing the fibers. The nuclei, usually numbering more than one in a muscle fiber, lie close along the inner surface of the sarcolemma. The muscle bundles are fastened together by a complex of connective tissue which carries elastic fibers, vessels, and nerves. When the muscle contracts, portions become double refractile, and electrical changes, which can be measured with special instruments, also take place. These reaction currents have been much studied of late for the elucidation of lesions of the muscle and the conducting systems.[3]

Specialized groups of fibers, known as muscle spindles, are found in the muscles of the trunks and extremities. These groups, which comprise about twenty fibers, are separated from the rest of the muscle by a connective-tissue capsule. They do not atrophy when the nerves leading to the muscle are cut, but may show degenerative changes under certain conditions, such as exophthalmic goiter. It has been thought that they are responsible for the muscle sense, but little is known as to their functions.

RIGOR MORTIS.

About two to four hours after death, coagulation of the protoplasm of the muscle fibers takes place, resulting in some shortening and stiffening of the muscle; this continues as a rule for forty-eight hours, and then disappears. It is much more marked in persons with abundant musculature, as it is dependent upon the amount of protein in the fibers.

[1] For details concerning the minute structure of muscle fibers, see *Heidenhain*, Plasma und Zelle, Jena, 1911, ii, 507.

[2] *von Gierke, E.*, München. med. Wchnschr., 1911, lviii, 2315.

[3] For theories of muscular contraction, see *Verworn, M.*, Allgemeine Physiologie, 5th ed., Jena, 1909; and Irritability, Silliman Lectures, New Haven, 1913; *Robertson*, Quarterly Jour. Exper. Physiol., 1909, ii, 303; and *Lillie, R. S.*, Science, 1912, N. S. xxxvi, 247.

Hence, in persons with fatty or degenerated muscle fibers, rigor mortis is very slight or is absent; this is the case in phosphorus poisoning. After hemorrhage and poisoning with strychnine or potassium cyanide there is a very rapid and marked rigor mortis. (For further details see page 1215.)

NECROSIS.

Necrosis of muscle may be the local result of mechanical or chemical injury; it occurs in inflammatory foci, and may follow serious local disturbances of the circulation, as from pressure by tumors or cicatrices, etc. The muscle fibers may gradually lose their striations, become granular, and disintegrate, or the muscle substance may become homogeneous and strongly refractile and break into irregular masses. Necrotic muscle fibers are finally removed by the direct action of phagocytes or after various transformations leading to their solution.

ATROPHY AND HYPERTROPHY.

Simple Atrophy.—This may occur in old age, in prolonged exhausting diseases, or as a result of inactivity, pressure from a foreign body, tumors,

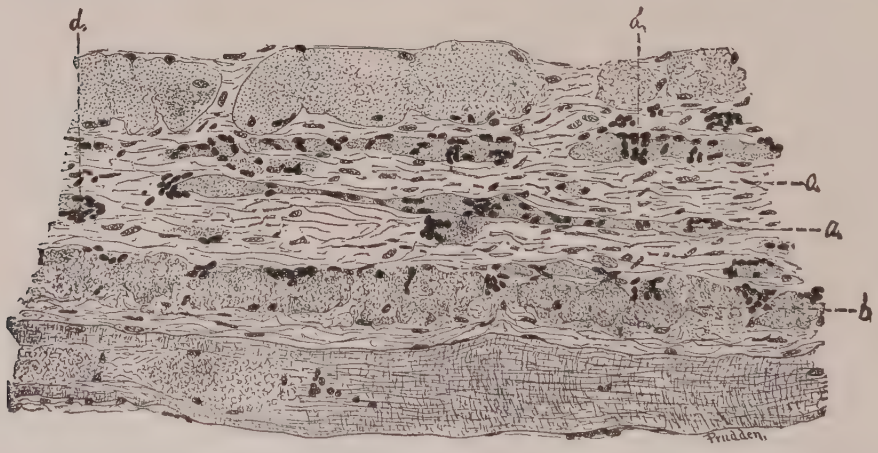


Fig. 724.—Progressive Muscular Dystrophy (Soleus muscle, longitudinal section). *a*, Atrophied muscle fiber; *b*, degenerated muscle fiber; *c*, interstitial tissue; *d*, clusters of proliferated muscle nuclei.

etc. Arthritic muscular atrophy due to acute or chronic inflammations of the joints belongs here, as the reflex inhibition of muscular movements owing to the inflammatory joint changes practically immobilizes the muscles attached to the part. The muscle fibers grow narrower, the degree of narrowing frequently varying considerably in different parts. They usually retain the striations, but these may be obscured by degenerative changes. The sarcolemma may become thickened, and there may be a considerable increase in connective tissue between the muscle fibers and bundles. Brown pigment particles may accumulate in the

atrophied fibers.[1] Nerve degeneration and anterior root changes may follow simple atrophy.

Muscular atrophy in some cases follows injuries or overstraining of groups of muscles, and may occur as one of the sequelæ of typhoid fever and diphtheria.

Neurotic Atrophy.—This occurs when the nerves leading to the muscle are injured, and may follow lesions of the brain or spinal cord. Just how much the atrophy is dependent upon the nerve lesion and how much upon the enforced inactivity of the muscle is still under discussion. The muscles which have atrophied under the influence of a simple neuritis can be kept in fair condition by massage and electrical treatment. The atrophy following cerebral injuries is much slower than that induced by spinal or peripheral nerve lesions.

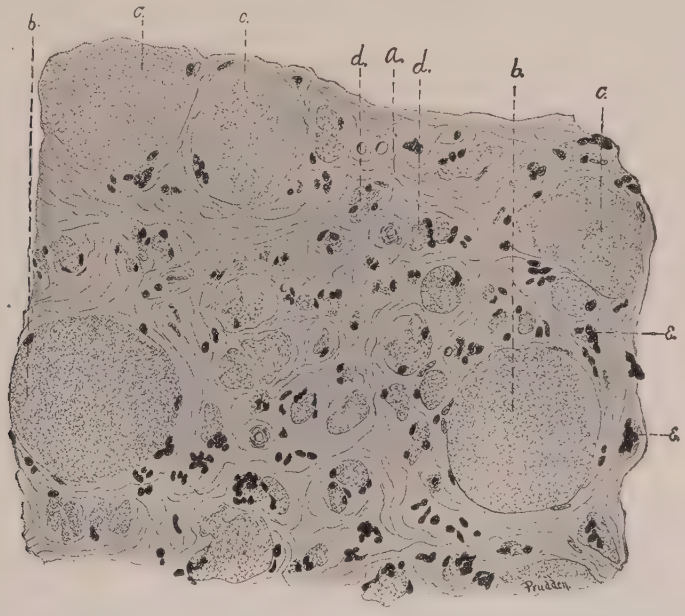


Fig. 725.—Progressive Muscular Dystrophy (Soleus muscle, transverse section). *a*, Increased interstitial tissue; *b*, nearly normal muscle fibers; *c*, degenerated muscle fibers; *d*, atrophied muscle fibers; *e*, clusters of proliferated muscle nuclei.

Progressive muscular atrophy of the Duchenne-Aran type is dependent upon nerve changes, even though the latter are accompanied by disease of the anterior horn cells (see page 1167).

Progressive Muscular Dystrophy.—This lesion consists essentially in a combination of simple or degenerative atrophy of the muscle fibers with chronic interstitial inflammation, and is sometimes associated with proliferative changes in the muscle nuclei, which may lead to a temporary hypertrophy of the fibers. In the earlier stages of the disease the muscles may be pale and soft, but otherwise exhibit to the naked eye but little

[1] *Ishida, M.*, Virchows Arch., 1912, ccx, 67.

alteration. Gradually, however, the muscle substance becomes replaced by connective tissue, so that in marked and advanced cases the muscles are converted into fibrous bands or cords, whose cicatricial contraction may induce great deformities.

Microscopical examination shows in the early stages of the disease a proliferation of cells in the interstitial tissue, so that this may have the appearance of granulation or embryonal tissue, and, in some cases, marked proliferative changes in the muscle nuclei (Fig. 724), leading to the formation of new cells which may more or less replace the contractile substance within the sarcolemma. The new interstitial tissue increases in quantity and grows denser, and may crowd the muscle fibers apart (Fig. 725). The walls of the blood-vessels also may become thickened. Hand-in-hand with these interstitial alterations the atrophy of the muscle fibers proceeds. These may simply grow narrower, retaining their striations; or they may split up into longitudinal fibrillæ, or transversely into discoid masses, and in this condition disappear. In other cases a certain amount of fatty or hyaline degeneration may be present. These degenerative and proliferative changes do not, as a rule, occur uniformly in the affected muscles, but some parts are affected earlier and more markedly than others. The atrophied muscle may be replaced by fat. This fatty alteration may be so extensive that the muscle is larger than normal, producing what has been termed a pseudohypertrophy. In such tissues the muscle fibers may be so infrequent that it is difficult to find them microscopically.

Progressive muscular dystrophy is apt to commence in the small muscles of the extremities, in many cases in the muscles of the ball of the thumb. It may commence in the muscles of the shoulder, the arms, or the back. It may have a continuous extension, or it may jump single muscles or groups of muscles. Death may be induced by the affection of the muscles of respiration or deglutition.

The causes of this lesion are in many cases unknown, and there is considerable lack of unanimity of opinion as to whether it is primarily a disease of the muscles or of the nervous system. In a considerable proportion of cases the muscle lesion is associated with atrophy of the ganglion cells in the anterior cornua of the spinal cord and the development of connective tissue about them. These changes, however, may be secondary to the general disease and not the cause of the atrophy.[1] In other cases these changes in the cord may apparently be absent. Recently the theory has been promulgated that muscular dystrophy may originate as a result of abnormal functioning on the part of the endocrine glands, leading in the muscle fibers to a defective storage of glycogen, the carbohydrate which is the source of muscular energy. The sugar content of the blood is low, and the creatin in the urine is increased.[2]

It is probable that there are a number of types of progressive muscu-

[1] *von Werdt, F.*, Frankfurt. Ztschr. f. Path., 1908, ii, 577.

[2] *Janney, N. W., Goodhart, S. P.*, and *Isaacson, V. I.*, Arch. Int. Med., 1918, xxi, 188; *McCrudden, F. H.*, ibid., p. 256; *McCrudden, F. H.*, and *Sargent, C. S.*, ibid., 1916, xvii, 465; and 1918, **xxi**, 252; *Timme, W.*, Arch. Int. Med., 1917, xix, 79 (bibl.).

lar dystrophy, which our present knowledge does not enable us clearly to distinguish.[1]

Myasthenia Gravis.—This is a rare disease in which there is weakening and ultimate paresis of the striated muscles of the body without constant changes in the nervous system.[2] The disease often begins with ptosis due to paralysis of the eye muscles; very frequently, also, the muscles of the face, larynx, and neck are involved, and as the disease progresses other groups of muscles may be affected. The important clinical symptom is the rapid exhaustion of the muscles under faradic stimulation.

Of the causes of the disease almost nothing is known, though a history of infection can be obtained in about 20 per cent. of the cases, and enlargement of the thymus has been reported in nearly 50 per cent.[3] A relationship between the condition and changes in the thyroid, parathyroids, suprarenals, and hypophysis[4] has been suggested.

The muscle fibers are usually normal; but in almost all cases a lymphocytic infiltration may be observed. A moderate fatty degeneration is probably dependent upon the slight atrophy which occasionally occurs. Edema and atrophy belong to the later phases of the disease.

Atrophia Musculorum Lipomatosa (Pseudohypertrophy of the Muscles).—In some cases, hand-in-hand with the production of new connective tissue in the muscles and the atrophy of the muscle fibers, or after these changes have made considerable progress, there occurs a development of fat tissue between the fibers (Fig. 726) which may disguise any diminution in the size of the muscles, or in some cases may even give them the appearance of a great increase in size. This condition is of most frequent occurrence in children, and is most apt to appear in the gastrocnemii muscles. In the upper extremities the deltoid and triceps are most frequently involved. The lesion may be symmetrical, affecting similar muscles on both sides of the body, or it may be unilateral. Parts of muscle bellies may be affected.

The cause of this form of atrophy is not definitely known. Various lesions of the spinal cord have been described as occurring with it; but, in many cases at least, alterations of the nervous system cannot be detected. A case[5] has been described in which this lesion was marked in the gastrocnemii in connection with multiple false neuromata. Some of these cases undoubtedly belong to the pseudohypertrophic types of muscular dystrophy.

Hypertrophy.—True hypertrophy of muscle as a pathological condition is rare, but it has been described in a few cases. It is usually confined to circumscribed groups of muscles. On microscopical examination the diameter of the fibers is increased, sometimes considerably,

[1] *Timme, W.*, Arch. Int. Med., 1917, xix, 79 (bibl.). For details of classification and lesions, see the standard textbooks on neurology, and especially the monographs of *Marburg* and *Jendrasski*, in Lewandowsky, Handbuch d. Neurologie, Berlin, 1911, ii, part 1, pp. 278 and 321.

[2] *Mandlebaum, F. S.*, and *Celler, H. L.*, Jour. Exper. Med., 1908, x, 308 (bibl.); *Patrick, H. T.*, Jour. Am. Med. Assn., 1902, xxxviii, 58; *Marburg, O.*, Ztschr. f. Heilk., 1907, xxviii, 111; *Bramwell, B.*, Brit. Med. Jour., 1901, ii, 769.

[3] For a report of a case of myasthenia gravis with thymoma, see *Jones, W. A.*, Jour. Am. Med. Asen., 1916, lxvii, 1354.

[4] See *Tilney, F.*, Neurographs, 1907, i, 920.

[5] *Prudden*, Am. Jour. Med. Sc., 1880, lxxix, 134.

though not uniformly. The transverse striation is unaltered and the muscle nuclei are in some cases enlarged. The cause of the change is unknown.

Such an hypertrophy occurs in myotonia congenita (Thomsen's disease) there being an increase in the size of the fibers and in the number of the nuclei. The transverse striations are less visible than normal; some fibers also show vacuolation. Clinically, the muscles are rigid when an attempt is made to contract them. The disease often occurs in several members of a family.

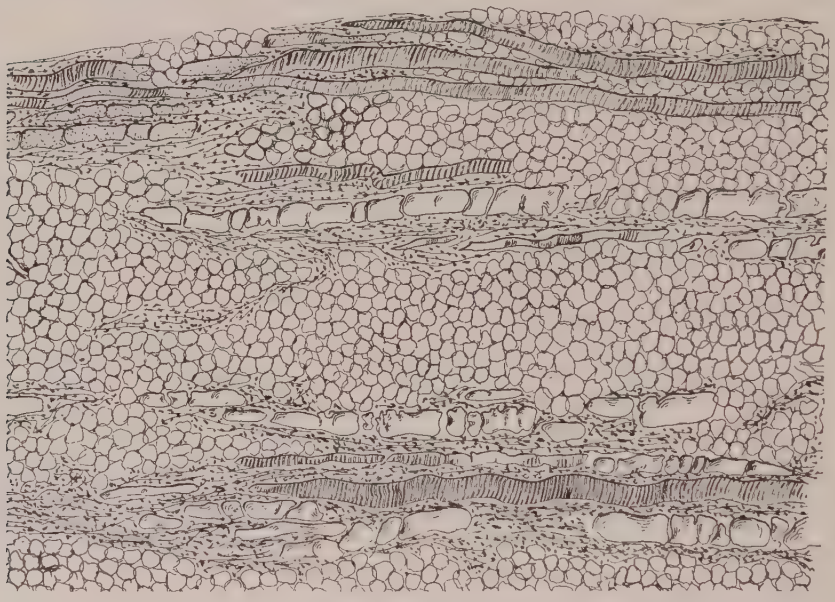


FIG. 726.—PSEUDOHYPERTROPHY OF GASTROCNEMIUS MUSCLE (FATTY INFILTRATION). The specimen is from the case mentioned on page 1055, accompanying multiple neuroma.

DEGENERATION.

Albuminous Degeneration of striated muscle occurs as a mark of toxemia in acute infectious diseases, and may lead to fatty degeneration.

Fatty Degeneration, with greater or less destruction of the muscles, may commence with a simple swelling and fine granulation of the fibers. As the process goes on, smaller and larger fat droplets appear in the contractile substance, which loses its striations and becomes friable and may be entirely destroyed, leaving within the sarcolemma a mass of fatty detritus which may finally be absorbed and disappear. This alteration may occur in acute parenchymatous myositis in connection with various forms of atrophy, in prolonged exhausting diseases, and in phosphorus poisoning. It occurs, also, after transverse lesions of the spinal cord.[1]

Fatty Infiltration of the muscle may occur in obesity and in alcoholics.

[1] *Zipkin, R.*, Virchows Arch., 1906, clxxxv, 478.

Hyaline Degeneration.—Under a variety of conditions the muscle fibers undergo a series of changes, leading to their conversion into a translucent, highly refractile material, somewhat resembling amyloid, but not giving its microchemical reactions, and apparently more nearly allied to hyaline material. The lesion in the muscle which we are considering is often called *waxy degeneration*, from the peculiar appearances which the muscles present.[1] When the lesion is far advanced and extensive the muscles are brittle and have a grayish-yellow, translucent appearance. Microscopical examination of various stages of hyaline degeneration of muscle shows that the contractile substance of the fibers becomes at first swollen and granular, and is gradually converted into hyaline material which may present the outlines of the swollen fibers, but is more frequently broken into larger and smaller shapeless clumps (Fig. 727).

Fig. 727.—Hyaline Degeneration (So-called Waxy Degeneration) of Abdominal Muscle in Typhoid Fever.

which may disintegrate and finally be absorbed. Hand-in-hand with these changes there usually occurs an increase in the interfibrillar connective tissue, and in certain cases there may be a proliferation of the muscle nuclei and a new formation of variously shaped cells within the sarcolemma which lead to the regeneration of the fibers. As a result of the brittleness of the degenerated muscles they are apt to rupture, and in this way hemorrhage may occur.

This form of degeneration may occur in progressive muscular atrophy, in various infectious diseases, in trichinosis, with local inflammation, injuries, freezing, etc. It is, however, most marked and frequent in typhoid fever. In this disease the rectus abdominis and the adductors of the thigh are most frequently affected.

Experimental investigations have shown that, under certain conditions, very similar appearances may be produced in the muscles by post-mortem changes, and by contractures due to strychnine poisoning and to high voltage electric currents.[2] Various changes—some of them necrotic—are at present incorrectly included under the name "hyaline degeneration of the muscles."

True **amyloid degeneration** is rare.

A peculiar degeneration with atrophy of the striated muscle of the

[1] For an experimental study of the so-called waxy or Zenker's degeneration of muscle, see *Thoma*, Virchows Arch., 1906, clxxxvi, 64.

[2] *Schmidt, M. B.*, Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, 218.

uvula has been described, in which a series of bleb-like structures form along the fibers, which they may finally replace.[1]

Calcification of individual muscle fibers is seen after blows or incised wounds, but is of rare occurrence.[2]

Serous or Hydropic Infiltration of muscle fibers occurs under various conditions in association with other lesions. Larger and smaller spaces filled with clear fluid are present between the fibers and often over small areas largely replacing them. Such fluid-filled spaces are often called vacuoles.

INJURIES, HEMORRHAGE, AND INFARCTION.

Wounds and Rupture.—When the muscle fibers are severed by wounds or rupture there is more or less degeneration of the divided fibers, and the wound may heal by the production of granulation tissue, which gradually becomes converted into cicatricial tissue, thus binding the severed parts together. In some cases there is a moderate new formation of muscle fibers (page 88).[3] When the wound does not gape, so that the severed ends are not much separated, there may be, it would seem, a direct re-establishment of muscular continuity by new development of muscle, without the formation of much new connective tissue.

Hemorrhage.—This may occur as a result of mechanical injury, from rupture of the fibers by convulsive contraction, as in tetanus, when the muscle fibers are degenerated, as in typhoid fever, or in connection with certain general diseases, as scurvy, purpura, hemorrhagic diathesis, septicemia, etc. The blood is usually readily absorbed.

Embolic Infarction of Muscles in connection with heart disease has been described in a few cases, but it is rare.

INFLAMMATION. (Myositis.)

Suppurative Myositis.—In the early stages of this lesion the muscle is hyperemic and edematous, and the interstitial tissue more or less infiltrated with small spheroidal cells. If the inflammation becomes intense there may be an excessive accumulation of pus cells, either diffusely in the interstitial tissue or in larger and smaller masses. Hand-in-hand with this cell accumulation occur degenerative changes in the muscle fibers. By pressure their nutrition is interfered with and they undergo granular, fatty, or hyaline degeneration, and necrosis. They may completely disintegrate; or gangrene may occur, so that larger and smaller masses of the infiltrated muscle tissue become soft and foul-smelling, and are converted into a mass of detritus in which but little muscle structure can be detected and which is intermingled with bacteria. In other cases there may be larger and smaller abscesses formed in the muscle, the muscle tissue itself degenerating and disintegrating and mixing with the contents of the abscess, or being pressed aside and undergoing atrophy and degeneration. In some cases, when the formation of pus is moderate

[1] *Hoen, A. G.*, Jour. Exper. Med., 1898, iii, 549.

[2] *Pielsticker, F.*, Virchows Arch., 1909, cxcviii, 374 (bibl.).

[3] *Schmincke, A.*, Zieglers Beitr., 1909, xlv, 424; *Pielsticker, F.*, Virchows Arch., 1909, cxcviii, 385 (bibl.).

in amount, there may be restoration by formation of granulation tissue between the muscle fibers. This becomes gradually dense and firm, and leads to more or less atrophy of the muscle fibers by pressure.[1]

Acute suppurative myositis may accompany wounds; it is very common in acute phlegmonous inflammations of the skin and subcutaneous tissue, and often accompanies acute infectious diseases, such as pyemia, erysipelas, etc. In most cases the "pyogenic" cocci are present in the inflammatory foci. Suppuration not infrequently occurs in the muscles adjacent to the inflamed mucous membranes in diphtheria.

Chronic Interstitial Myositis.—In this lesion there is a new formation of connective tissue between the muscle fibers or bundles of fibers. This new tissue is sometimes very cellular, resembling granulation tissue, and probably represents an early stage of the disease. In other cases (Fig. 728) dense cicatricial tissue crowds the muscle fibers apart, inducing atrophy in them, and sometimes leading to their complete destruction. This lesion, the analogue of chronic interstitial inflammation of the internal organs, may occur in muscles adjacent to other parts which are the seat of chronic inflammatory processes. It may occur in muscles which are not used. The new formation of fibrous tissue seems in some cases to be secondary to atrophy of the muscle fibers. In this case it would more appropriately be called *replacement fibrous hyperplasia.* Rheumatism is a frequent cause, as is also rupture of the muscle. The congenital wry neck or *caput obstipum* is a fibrous myositis due to rupture of the sternocleidomastoid during delivery.

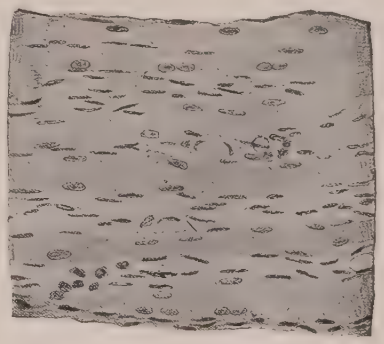


Fig. 728.—Chronic Interstitial Myositis.

Primary Acute Polymyositis.—Several observers[2] have described an affection involving swelling of the muscles of the tongue, back, and extremities, with local pain and fever. Voluntary movement is lost, and various rashes of the skin may occur (*dermatomyositis*). The muscles are brownish red in color, with yellowish spots; hemorrhages, and foci of hemorrhagic exudates with many leucocytes are present. There is degeneration of the muscle fibers. The disease may become chronic, and may be fatal. It is believed to be due to some form of autointoxication and may be associated with some infective focus in the body or with rheumatism.

Myositis Ossificans.—Under conditions as yet imperfectly understood, there occasionally occurs, most often in young persons, a condition known as *myositis ossificans progressiva multiplex.*[3] The process begins

[1] See *Lorenz, H.*, Die Muskelerkrankungen, Nothnagel, Spez. Path. u. Therap., Vienna, 1904, 11^3, 1.

[2] See *v. Strümpel*, Deutsch Ztschr. f. Nervenh., 1891, i, 479; *Mayesima*, Deutsch. Ztschr. f. Chir., 1910, civ, 318; *Unverricht*, Deutsch. med. Wchnschr., 1891, xvii, 41.

[3] For a study of myositis ossificans, consult *Goto, S.*, Arch. f. klin. Chir. (Langenbeck), 1912–13, c, 730; *De Witt, L.*, Am. Jour. Med. Sc., 1900, cxx, 295 (bibl.); *Kidner, F. C.*, Jour. Am. Med. Assn., 1917, lxviii, 177 and *Rosenstirn, J.*, Ann. Surg., 1918, lxviii, 485.

in the fasciæ, aponeuroses, tendons, or periosteum, and involves the muscles only secondarily. Three stages of the lesion can usually be made out: (1) A connective tissue hyperplasia; (2) a sclerosis of this connective tissue; and, (3) a formation of cartilage and bone in the sclerosed area. The bone is practically normal in structure. The muscle fibers undergo secondarily a greater or less degree of atrophy or degeneration. There may be fatty infiltration between the fibers, and various deformities are produced by the shortening and progressive immobility of the affected parts.

While inflammatory processes, including syphilis, can be ruled out as causes of the disease, trauma is certainly important; on the other hand, masses of bone may form spontaneously with no antecedent history of injury.

While the above disease is a progressive and frequently a general one, there may be a local new formation of bone in muscle as a result of prolonged or repeated mechanical irritation. Thus, in the adductors of the thigh in persons who are constantly in the saddle, or in the deltoid muscle soldiers who strike this part with their weapons in drill, there may be a formation of bone.[1] In these instances the new growth of bone is dependent upon inflammatory processes leading to the formation of connective tissue which is later metaplastically altered into bone. The periosteum plays no part in the process unless the bone growth is directly in contact with this membrane.

Tuberculous or Syphilitic Inflammation in the muscle is of occasional occurrence; the active processes are in the connective tissue and blood-vessels, the muscle fibers being secondarily involved in various phases of atrophy and degeneration.

TUMORS.[2]

Muscle tumors, which are rare, may be divided into three types: (1) Those developing in smooth muscle cells (**leiomyoma**); (2) those developing in striated muscle cells (**rhabdomyoma**); and (3) those developing in the connective tissue of either variety of muscle.

The most common site for the leiomyoma is the uterus, where it is the most frequent of all tumors (page 429). It is found also in other parts of the genitourinary tract, *e.g.*, in the kidney,[3] and in the gastrointestinal tract[4] and the skin.[5]

For a discussion of rhabdomyoma, see page 431.

Malignant tumors arising in the muscle itself are sometimes called sarcomata,[6] though there is a considerable body of opinion in favor of retaining this term for tumors of connective tissue; and it would perhaps be better, therefore, to employ some such term as *myosarcoma* or *malignant myoma*[7] (page 431). In employing the latter term, however, one

[1] See *Gruber*, Über Histologie u. Pathogenese der circumskripten Muskelverknöcherung, Jena, 1913.

[2] For a discussion of tumors of muscle, see *Busse*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix[1], 1226 (bibl.); *Thorel*, ibid., 1901, vi, 742 (bibl.).

[3] *Neurnberg*, Frankfurt. Ztschr. f. Path., 1917, i, 433 (bibl.).

[4] *Anitschkow*, Virchows Arch., 1911, ccv, 243.

[5] *Lieber*, Zieglers Beitr., 1915, lx, 449 (bibl.).

[5] *Landois*, Berl. klin. Wchnschr., 1912, xlix, 2274 (bibl.).

[7] *Ghon* and *Hintz*, Zieglers Beitr., 1909, xlv, 89 (bibl.).

should not lose sight of the fact that, in the last analysis, malignancy is a clinical phenomenon, and is not necessarily correlated with the morphology of the tumor.

Most new growths arise in the connective tissue of the muscle, where there have been found **hemangioma,**[1] **lymphangioma,**[2] **fibroma,**[3] **lipoma,**[4] **chondroma,**[5] and **chondrolipoma.**[6]

The **desmoid**[7] is an extremely hard fibroma which in rare cases may be multiple. It arises from the fasciæ of the abdominal wall, most often from the sheath of the rectus muscle, and is found almost exclusively in women, particularly after repeated childbearing.

Secondary tumors of muscle originate nearly always by extension, rarely by metastasis from a distant growth.[8]

PARASITES.

Trichinella spiralis is the most common parasite in the muscles and incites an acute myositis by invasion of the muscle fibers. The sarcolemma remains, and the irritating excretions of the parasite set up an inflammatory reaction with involvement of the surrounding fibers and the determination to the site of many eosinophile cells. Ultimately, the fibrous capsule becomes dense, the exudate disappears, and calcification sets in about the dead parasite.

Cysticercus cellulosæ and **echinococcus** occasionally occur.

[1] *Serra*, Arch. f. klin. Chir. (Langenbeck), 1913–14, ciii, 1018; *Borchard*, Zieglers Beitr., 1914, lvii, 30.
[2] *Ritschel*, Beitr. z. klin. Chir. (Bruns), 1895–96, xv, 99 (bibl.).
[3] *Bidone*, Monatschr. f. Geburtsh. u. Gynäk., 1899, ix, 336.
[4] *Morestin*, Bull. Soc. anat. de Paris, 1897, lxxii, 939; *Fraikin*, Jour. de méd. de Bordeaux, 1897, xxvii, 573.
[5] *Honsell*, Beitr. z. klin. Chir. (Bruns), 1899, xxiii, 210 (bibl.).
[6] *Kollaczek*, Beitr. z. klin. Chir. (Bruns), 1908–09, lxi, 127 (bibl.).
[7] *Pfeiffer*, Beitr. z. klin. Chir. (Bruns), 1904, xliv, 334 (bibl.); *Andrews*, Surg., Gynec., and Obst., 1911, xii, 190.
[8] For an account of the changes produced in muscle fibers by invading tumors, see *Fujinami*, Virchows Arch., 1900, clxi, 115 (bibl.).

CHAPTER XIII.

THE BONES AND JOINTS.

The Bones.

General Considerations.

It is not possible to understand the changes which the bones suffer under various abnormal conditions unless one holds in mind the physical peculiarities of this form of connective tissue and the ways in which the dense and solid structure is formed and dissolved and re-formed in the processes of development and growth.

The striking character of bone, adapting it to serve as the supporting framework of the body, is the association with its organic tissue of the inorganic salts to which its hardness and solidity are due. But it is through connective tissue and blood-vessels and under the agency of highly specialized connective-tissue cells—*osteoblasts*, the "bone-builders," and *osteoclasts*, the "bone-destroyers"—that bone is formed and during life ceaselessly remoulded.[1]

The general pathological processes to be observed in bone are fundamentally similar to those in the soft tissues of the body. Disturbance of circulation, necrosis, degenerations, inflammation, tumors, etc., are common. But their manifestations are modified and often complicated and obscured in part by the hardness of texture and durability of bone tissue, and especially by the frequent participation in the processes of the osteoblasts and osteoclasts.[2] Thus it is that many abnormalities of the circulation and their sequelæ are less obvious than in other parts of the body; necrosis is masked by appearances due to the inorganic elements; while many of the inflammatory processes and tumors are regularly associated with the formation of new bone in such mass and measure as often to distort the bone and greatly complicate the picture.

We have seen repeatedly, in studying the lesions of the viscera, that the primary pathological processes are modified by the tissues in which they are active. Attention is called to this feature in bone only because the regional modification is here so conspicuously marked that one is liable to lose sight of the unity of the fundamental processes and erroneously to conceive that the pathology of bone is a subject especially obscure, complex, and difficult.[3]

ANOMALIES OF BONE DEVELOPMENT.

Deficient Growth of Bone.

Dwarfism.—This may be either local or general. In the former case it leads in children to shortening of the extremities when the epiphyseal cartilage is injured by trauma or by inflammation. Localized disease of the brain or cord may cause a local checking of the growth of the face or extremities. General interference with bone growth leads to a reduction in size of the skeleton, which may be symmetrical, as in the true dwarfs, or distorted, as in the achondroplastic or cretinistic dwarfs.

[1] *Hofmeister, F.*, Ergebn. d. Physiol. (Asher-Spiro), 1910, x, 435.

[2] *Keith, A.*, Lancet, 1918, i, 250.

[3] For résumé and bibl. of the pathology of bone, see *Schmidt, M. B.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1897, iv, 531; 1898, v, 895; and 1900–01, vii, 221.

The skull of the true dwarfs is apt to be somewhat large in proportion to the height of the body, but as ossification proceeds at a normal rate the brain is not injured; hence, the intelligence is usually good. As the bone failure in the achondroplastics is in the cartilaginous portion, the membranous bones of the calvarium may develop normally, and the intelligence be normal. The cause of the diminished bone production is not known. Hypophyseal lesions have been found in a number of cases.[1] In cretinism the idiocy is due to the athyreosis rather than to any lesions of the bones of the skull.

Other forms of dwarfism are due to well recognized causes, among which are rickets (page 1072) and the nutritional defect known as infantilism.[2] In the latter, various conditions have been suggested as factors, including defective digestion with poisoning from abnormal intestinal putrefaction, lack of secretion of the pancreas, insufficiency of the pituitary gland. The children are symmetrically small, and suffer from feeble digestion and delayed ossification of the bones. The latter are not fragile, but bend easily and green-stick fractures are not infrequent.

Brain lesions, such as microcephalia, hydrocephalus, porencephalia, and mongolism, are often associated with dwarfism.[3]

Achondroplasia (Chondrodystrophia Fetalis).—If the normal proliferation of the cartilage of the long bones is checked, the limbs will not reach their usual length, while the growth of the other bony structures of the body will not be impeded. In achondroplasia, the inhibition of growth takes place before birth, and the disease is often so advanced that the child dies early. If it survives, the upper part of the skull grows normally so that the head is large in proportion to the height (Fig. 729). The base of the skull may remain much smaller than normal, in some, but not all, instances because of premature synostosis of the sphenoid and occipital bones, which causes a sinking in of the bridge of the nose. The bones of the limbs, while short, develop fully in a lateral direction, and thus become even thicker than the corresponding normal bones. The muscles are often well developed; and these achondroplastic dwarfs when mature frequently possess great physical strength. The trunk is usually normal in size. The fingers are often flat and stumpy (Fig. 730). The thyroid gland is normal, showing that the disease has no relationship with cretinism, and that the changes in the bones are not those of rickets; it is, therefore, incorrect to use the term, *fetal rickets*.[4]

Osteogenesis Imperfecta (Fragilitas Ossium; Osteopsathyrosis).—In this disease, which is both hereditary and congenital, the osteoblasts of the internal and external periosteum form an imperfect type of bone. As the epiphyseal cartilages perform their functions properly, the bones are of normal length or nearly so, but the medullary cavity is large, the shaft thin, porous, and very fragile. Fractures may occur, and even undergo

[1] *Benda, C.*, Berl. klin. Wchnschr., 1900, xxxvii, 1205; *Hueter, C.*, Virchows Arch., 1905, clxxxii, 219.

[2] *Herter, C. A.*, On Infantilism from Chronic Intestinal Infection, New York, 1908; and *Strauch, A.*, Am. Jour. Med. Sc., 1914, cxlviii, 247.

[3] For further details, see page 499.

[4] See, for further details, *Kaufmann, E.*, Zieglers Beitr., 1893, xiii, 32; *Sumita, M.*, Deutsch. Ztschr. f. Chir., 1910, cvii, 1 and *Wheeldon, T. F.*, Am. Jour. Dis. Child., 1920, xix, 1 (bibl.).

repair, before birth. If the child survives, which is rare, the bone fragility, or osteopsathyrosis, may last for years or may gradually disappear.[1] While dwarfism is frequent, some affected individuals may be of short

FIG. 729.—ACHONDROPLASIA.
Showing shortened and deformed arms and legs, the trunk and head being approximately normal.

stature only, others of normal height. Easy fracturability of the bones may be evident also in juvenile osteomalacia (page 1071).

FIG. 730.—ACHONDROPLASIA.
Showing characteristic deformity of the hands. (Photograph by Dr. Northrup.)

Cretinism and Myxedema.—Dwarfs in whom the condition is due to absence of thyroid secretion show deformities similar to those seen in

[1] *v. Recklinghausen, F.*, Untersuchungen über Rachitis u. Osteomalacie, Jena, 1910; *Paltauf*, Ueber den Zwergwuchs, Vienna, 1891; *Bronson, E.*, Edinburgh Med. Jour., 1917, xviii, 240 (bibl.).

achondroplasia—the shrunken nose and the short thick limbs (page 1063). The epiphyseal cartilages functionate imperfectly, and may remain unossified for many years.[1] As is well known, the exhibition of thyroid gland will often cause a considerable bone growth, though this is not limited to cretins but may affect normal bones also.[2] In congenital or infantile myxedema the same bone changes appear, but to a lesser extent.

Excessive Growth of Bone.

Gigantism.—This may be general or partial. The normal limits of height may be placed as about two meters; but a few symmetrically developed giants are seen whose dimensions considerably exceed this, though usually the head is small in proportion to the body while the limbs are excessively long. The muscular development, as a rule, is poor; the bones are of imperfect quality; and spinal curvatures are frequent. In addition, evidences of status lymphaticus are sometimes present. No cause for the excessive size can be found, though a poor development of the generative organs is usual, and hypophyseal disease is probable.[3] A similar overgrowth is observed in those castrated in childhood, since under those conditions the hypophyseal secretions are increased and the epiphyseal cartilages retain their activity for a long period.[4] A large proportion of giants, however, are certainly acromegalics.[5]

Partial gigantism is the result of some stimulation of the growing bone. Various forms of inflammatory osteitis and arthritis excite bone growth, either directly or through hyperemia and venous congestion.[6]

Acromegaly.[7]—The skeletal changes which follow the growth of tumors in the anterior lobe of the hypophysis are not in any way peculiar to the disease. They are rather the expression of an increase in the physiological activity of the bone-forming elements which results in a corresponding augmentation in the volume of the bone structures. The bones grow in length and also in thickness. The muscle insertions undergo hyperplasia, so that they become prominent raised plateau-like areas. The thickening of the hands and feet, on the contrary, is due, as shown by skiagrams, only in a slight degree to an increase in the volume of the bones, most of the enlargement consisting of an increase in the soft parts. The changes in the skull are due to enlargement of the frontal and other sinuses which lead to prominence of the orbital and supraorbital ridges; while the widening of the sella turcica is due to the increase in the size of the hypophysis. The increase in the length of the lower jaw, which produces the remarkable prognathism, causing the lower teeth to project in

[1] *Dieterle, T.*, Jahrb. f. Kinderh., 1906, lxiv, 465, 576.

[2] *Bircher, E.*, Deutsch. Ztschr. f. Chir., 1909, xcviii, 75.

[3] *Falta, W.*, The Ductless Glandular Diseases, Philadelphia, 1915.

[4] *Tandler, J.*, Wien. klin. Wchnschr., 1910, xxiii, 459; *Sellheim, H.*, Beitr. z. Geburtsh. u. Gynäk., 1899, ii, 236.

[5] For further details, see page 498.

[6] *Wittelshöfer, R.*, Arch. f. klin. Chir. (Langenbeck), 1879, xxiv, 57; *Hofmann, M.*, Beitr. z. klin. Chir. (Bruns), 1906, xlviii, 391; *Wieland, E.*, Jahrb. f. Kinderh., 1907, lxv, 519.

[7] *Fischer, B.*, Frankfurt. Ztschr. f. Path., 1910, v, 351, 587; 1912, xi, 130; *Biedl, A.*, The Internal Secretory Organs, New York, 1913; *Leri, A.*, Lewandowsky, Handb. d. Neurologie, 1913, iii, 283 (very complete bibl.).

front of the upper, is due to new osseous growth from the periosteum. If the acromegaly begins late in life when the activity of the epiphyseal cartilages has ceased, the height may not be greatly influenced. The bone produced is often somewhat rarefied by partial absorption; in rare instances there may be a great increase in the density of the bone owing to the deposition of new osseous material.[1]

Hyperplastic Periostitis (Hypertrophic Pulmonary Arthropathy).—A peculiar periosteal osteogenesis affecting most frequently the terminal phalanges of the fingers and toes is observed in connection with chronic pulmonary tuberculosis, bronchiectasia, chronic empyema, chronic heart disease with much cyanosis, syphilis, chronic jaundice, and malignant tumors. The congestion and toxemia seem to be responsible for the incitement of the bony lesions.

The thickening causes the end phalanges to assume a globular shape, and the enlarged nails are noticeably curved over the tip of the phalanx. Skiagraphs of hands so affected show that only rarely is the bone extensively involved, the enlargement being due largely or entirely to thickening of the periosteum. When the accompanying disease is very chronic, other bones may show alterations, especially the peripheral extremities of the forearm and leg. The lesion is usually painless except when acute and the joints are not involved.[2]

Leontiasis Ossea.—This is a rare and but little understood disease, in which there is a diffuse thickening of the bones of the face and skull, the hypertrophy of the cheek bones, jaws, and orbital ridges giving the face the leonine expression which the name signifies. The closure of the foramina of the skull may cause paralysis, blindness, and loss of the sense of smell.

Microscopically, the enlarged bones are very dense and compact, the diploë often being obliterated. The thickness of the calvarium may be as great as four centimeters and the total quantity of bony material in the skull may be five times the normal. Whether the disease is the same as osteitis deformans (Paget's disease) is still in doubt.[3]

Osteitis Fibrosa (von Recklinghausen's Disease).—This is a lesion of the bone which results in a local destruction of osseous tissue. Parallel with the bone destruction goes the formation of new bony or osteoid material, and, in addition, the normal bone-marrow is replaced by a soft fibrous material somewhat resembling sarcoma. In the later stages of the process, hemorrhages are apt to occur in the new-formed tissue, about which a large number of multinucleated giant cells usually form. The structures so produced resemble very closely the giant-cell sarcomata, but differ from them in the fact that sooner or later the new-formed bony substance undergoes a more or less complete absorption with the formation of cystic areas containing a fluid of a dark brownish color due to the

[1] For other lesions of the disease, see page 496.

[2] *Janeway, T. C.*, Am. Jour. Med. Sc., 1903, cxxvi, 563; *Ebstein, P.*, Deutsch. Arch. f. klin. Med., 1906, lxxxix, 67; *Beuttenmüller, H.*, Berl. klin. Wchnschr., 1908, xlv, 1001 (icteric cases); *Krüger*, Virchows Arch., 1906, clxxxv, 43; *Marie, P.*, Rev. d. méd., 1890, x, 1; *Thompson, E. S.*, Med. Chir. Trans., 1904, lxxxvii, 85; *Corper, Cosman, Gilmore,* and *Black*, Am. Rev. Tuberc., 1921, 5, 357–387.

[3] *Schmidt, M. B.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1898, v, 895; *Koch, M.*, Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 107; *Bockenheimer, P.*, Arch. f. klin. Chir. (Langenbeck), 1908, lxxxv, 511.

deposition of blood pigment. In case no hemorrhage has occurred, the softened wall and the cyst contents are colorless. When the disease attacks one of the long bones, the formation of the cysts and the softening of the surrounding bony structures often permit spontaneous fracture, or in less severe cases marked bending or softening of the bone. Where the process involves the bones of the face or skull, cyst formation is unusual.

The lesions of osteitis fibrosa localize themselves most often in those portions of the bony system which are frequently injured by trauma. In the long bones, the most usual site is the diaphysis, though in younger persons the epiphysis may be most often involved. The most extensive tumors are usually those seen in the head of the tibia, where the growth projects in the form of rough masses which can be easily felt. The short bones of the feet and hands are very infrequently involved, the bones of the trunk much less often than those of the extremities. The clavicle is a frequent site, and the ribs are occasionally involved and may soften so that the thorax is altered in shape. The spinal column in severe cases may show considerable shortening. In the pelvis, spontaneous fractures are unusual, even though the tumor formation may be very extensive. A fairly frequent type occurs in the bones of the face, which may give rise to confusion with other forms of bony disease, such as Paget's disease (osteitis deformans) or leontiasis ossea. The upper or lower maxilla may be affected, and rarely the bones of the calvarium. Secondary changes are due to functional alterations in the muscles which may undergo atrophy and fatty degeneration owing to poor nutrition. The disease occurs most frequently in the second and third decade, in either a circumscribed or a generalized form, some cases diagnosed as leontiasis ossea belonging to the latter type. The circumscribed form involves either a portion of a bone, appearing in the form of a cyst most frequently when in the metaphyses of the lower extremities, or a considerable portion of the skeleton, especially all the bones of the face. Skiagraphs of the condition show the bones to be of a spongy structure with lighter portions where the cystic softening has occurred. The bone itself is atrophied and shows rough contours as if the osseous portion had been eaten away.

The disease may exist without any symptoms or may cause pain and a good deal of weakness. Attention is usually directed to it by the occurrence of a spontaneous fracture, which may heal satisfactorily, or the appearance of a considerable tumor. If the disease remains of a circumscribed type, it may cause no disturbance of health throughout life; but the generalized type usually leads to death in consequence of cachectic disturbances due to interference with bodily function. Only in exceptional instances has a true sarcoma developed in the tissues with general involvement of the body and death following extension of the growth.

Osteitis fibrosa must be differentiated from Paget's disease, osteomalacia, syphilitic bone disease, and tuberculosis. The first, which was previously regarded as identical with osteitis fibrosa, is quite different in its course. The deformity of the bone is much greater; and the extension of the disease is much more general throughout the skeletal system.

In fact, it is rather common to see Paget's disease involve almost all the bones; and for this reason general symptoms from the organs, such as the heart, kidney, and lungs, which are influenced by the occurrence of the bone changes, are apt to appear earlier in Paget's than in osteitis fibrosa, in which, indeed, they may never occur. Osteitis fibrosa, also, usually begins early, whereas Paget's rarely appears before the fortieth year. Paget's disease is especially apt to localize on the calvarium so that patients usually complain that their hats are too small; and bony fractures while common in osteitis fibrosa are rare in Paget's disease. The latter is apt to establish itself in a group of bones and then to involve others progressively, while osteitis fibrosa remains more or less confined to the bone originally attacked. Radiographically and microscopically, there is but little difference in the two lesions.

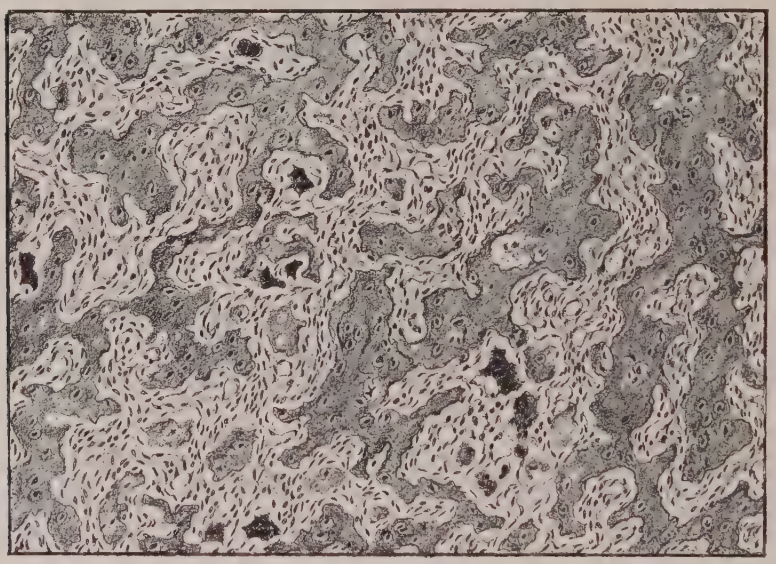


Fig. 731.—Osteitis Fibrosa.
Cellular type with giant cells.

Osteomalacia usually involves the bones of the pelvis symmetrically and early. The extremities are involved only when the deformity of the trunk has progressed very far. In osteomalacia the pains that interfere with movements are very early and well marked, whereas in osteitis fibrosa they are absent or slight, and may clear up. In osteomalacia, also, there is increasing abnormal flexibility of the bone itself, because new formation of bone tissue does not occur.

Bone syphilis occurring in periosteal form may produce lesions which have a great resemblance to those of osteitis fibrosa; in consequence of the rarefying osteitis there is a compensatory new production of bone which assumes the form of exostoses especially on the tibia, and these changes may be accompanied by spontaneous fractures and bending of

the bone which commonly are preceded by very severe pain. The pains of syphilis, however, are very much more severe during the night, and this observation, together with a positive Wassermann reaction, the history of the patient, and the *x*-ray picture, will permit of a diagnosis. In syphilis the parts attacked are peculiarly eaten out so that the bone may be described as worm-eaten.

Bone tuberculosis is not apt to be confused with osteitis fibrosa for the former more often occurs on the short bones of the hands or feet, and about the joints; and the formation of cold abscesses with sinuses and the general destruction of the bone without much attempt at repair will usually permit of a diagnosis. The development of sequestra, which is common in tuberculosis, does not occur in osteitis fibrosa.

Fig. 732.—Osteitis Fibrosa, Dense Type.

The differentiation from giant-cell sarcoma (Fig. 240, page 445) is not altogether easy, and the clinical history is very important for a diagnosis. In osteitis there is usually, in addition to the giant-cell portions (Fig. 731), other parts of the tumor which do not contain such cells (Fig. 732), and from these the diagnosis can be made. Mitoses are not found in the connective-tissue cells of osteitis fibrosa, as they are in the cells of the tumor, and metastases have not been noticed even when the growth has existed for ten years or more.[1]

Osteitis Deformans (Paget's Disease).—This is a chronic disease, affecting usually persons between the fifth and the eighth decennium. The process may be designated as an osteomyelitis fibrosa, and consists in the formation of a solid cellular connective tissue which replaces the bone substance and fills the medullary cavity. The destruction of the

[1] *Haberer, H.*, Arch. f. klin. Chir. (Langenbeck), 1907, lxxxii, 873; *v. Recklinghausen*, Untersuchungen über Rachitis und Osteomalacie, Jena, 1910; *Klestadt, W.*, Beitr. z. klin. Chir. (Bruns), 1911, lxxv, 681; *Michælis, M.*, Über Ostitis fibrosa, Inaug.-Diss., Berlin, 1913.

bone is accomplished not only by the osteoclasts, but also by invading blood-vessels and by halisteresis. Ultimately, poorly organized bone may form in the fibrous tissue. Sarcoma may ultimately develop.

The most frequent site is the skull, although the tibia and femur are often involved ultimately, and, as the disease advances, may enlarge, soften, and, finally, undergo marked anterior curvature from the weight of the body; spontaneous fractures, however, are rare. Spinal curvatures result from the softening of the bodies of the vertebræ. The bones of the skull thicken and enlarge, but are very spongy and may be pliable owing to the lack of lime salts. The bones of the face also enlarge, and confusion with leontiasis ossea may result.[1]

ANOMALIES OF METABOLISM.

Atrophy.—In old age or in senile conditions, the bones, especially those of the jaws, may become atrophied by the absorption of the hard tissue; the medullary spaces may be enlarged; the marrow tissue may contain less fat and may often be gelatinous in appearance. Senile kyphosis is often due to atrophy of the bodies of the vertebræ.

As the result of lack of use or from any cause which interferes with the nutrition of the bone, such as paralysis of the muscles or diseases of the joints, the bones may atrophy. Good examples of this are the conical shape assumed by bone ends after amputation and the bone shortening seen after poliomyelitic paralysis. Such atrophy after relatively slight injury has been shown by skiagraphs to be frequent[2] (see Fig. 748, page 1092).

The bone destruction may assume three types. The first is the result of the excess in the rate of physiological absorption by osteoclasts over that of the deposition of fresh bone by the osteoblasts; this is seen in pressure atrophy due to aneurysms or tumors, and is the process usually called rarefying osteitis. In the atrophy due to age, to inactivity, and to nerve lesions, there is a reduced osteoblastic new formation with a normal rate of osteoclastic destruction. The periosteum during these events may keep on building bone, so that the total volume appears greater though the weight per cubic centimeter may be less than that of normal bone.

The second type is due to the perforation of the bone by new-formed capillaries, though just how these cause the resorption is unknown. The process is usually limited to small areas, and regeneration of bone may fill all the absorbed areas.

The third process (*halisteresis*) begins with the removal of the lime salts of the bone; the resulting osteoid tissue is then dissolved. The phenomenon is seen chiefly in osteomalacia and rickets.

The bones, sometimes as the result of atrophy and sometimes from

[1] *Paget, J.*, Med. Chir. Trans., 1877, lx, 37; 1882, lxv, 225; *Stilling, H.*, Virchows Arch., 1890, cxix, 542; *Watson, W. T.*, Bull. Johns Hopkins Hosp., 1898, ix, 133; *Prince, M.*, Am. Jour. Med. Sc., 1902, cxxiv, 796; *Fitz, R. H.*, ibid., p. 814; *Vincent*, Maladie osseuse de Paget, Paris, 1904; *Higbee, W. S.*, and *Ellis, A. G.*, Jour. Med. Research, 1911, N. S. xix, 43 (bibl.); *Vogel, K. M.*, Med. Record, 1911, lxxx, 214; *Norrie, V. H.*, and *Wallace, G.*, Proc. New York Path. Soc., 1912, xii, 69.

[2] *Sudeck, P.*, Deutsch. med. Wchnschr., 1902, xxviii, 336.

causes which we do not understand, are unusually brittle and liable to fracture. The frequency of fracture of the hip in old persons is an example of such brittleness, the spontaneous fractures of tabes and syringomyelia are examples of the neurotrophic types of osteoporosis (see page 1070).[1]

Osteomalacia.—This lesion consists of the softening of fully formed hard bone tissue by the removal of its inorganic salts (*halisteresis*) with, at the same time, a moderate amount of new formation of osteoid tissue.[2] To this regenerative process is due the repair of fractures by callus occasionally seen in the osteomalatic. The rare form of osteomalacia occurring in children[3] is to be distinguished from rickets, whose lesions are due to a faulty development of bone, although in certain external characters and even in some histological processes the two diseases sometimes present considerable similarity. Osteomalacia usually occurs in adult females during pregnancy and after parturition; more rarely, it occurs in males, in females unassociated with the above conditions, and in children. A senile type is infrequent.[4]

Microscopical examination shows that the decalcification occurs first in the periphery of the Haversian canals and in the inner layers of the walls of the marrow spaces. As the salts of lime are removed, the basement substance at first remains as a finely fibrillated material, still preserving the original lamellation; the bone cells may be changed in shape or degenerated. After a time the decalcified tissue may disintegrate and be absorbed, and its place may be occupied by new-formed marrow or granulation tissue. As the disease goes on, the medullary tissue is congested and red, the fat is absorbed, and there is a great accumulation of marrow cells; or the marrow may assume a gelatinous appearance. The decalcification and absorption of the bone from within may proceed so far that the bony substance in the cancellous tissue almost entirely disappears, and the compact bone is reduced to a thin, soft, decalcified tissue inclosed in the periosteum. The disease is not always continuously progressive, but may be subject to temporary cessation.

Nothing definite is known as to its causation except that a considerable percentage of cases are coincident with pregnancy. Removal of the ovaries has resulted in some instances in a cure of the disease.[5]

As a result of the softened condition of the bones, the weight of the body and the actions of the muscles may induce a series of deformities which are sometimes excessive: curvatures of the spine, complete and incomplete fractures of the bone; distortions of the pelvis, sternum, etc. There is a tendency to a general involvement of the bones, but the changes are sometimes confined to single bones or to groups of bones. The cranium is rarely much affected, and when it is diseased the lesion is at the base. In the puerperal type, the first symptoms point to the pelvis as the usual site of the lesion. In males and non-parturient females, the

[1] For neuropathic types, see *Grunert*, Deutsch. Ztschr. f. Chir., 1905, lxxvi, 254.

[2] *Ribbert*, Anat. Untersuch. über die Osteomalacie, Bibl. Med., 1893, Abt. C., H. 2; *v. Recklinghausen*, Untersuchungen über Rachitis u. Osteomalacie, Jena, 1910.

[3] *Schmidt, M. B.*, Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 3.

[4] *Weber, O.*, Virchows Arch., 1867, xxxviii, 1.

[5] *Fehling, H.*, Arch. f. Gynäk., 1891, xxxix, 468.

spinal column and thorax are first affected, and there is usually a rapid spread to other parts of the skeleton.

Rachitis (Rickets).—Rickets is a metabolic disease whose manifestations are chiefly in the osseous system[1] evidenced by abnormal ossification. It occurs usually during the first two years of life, but may be seen as late as the twentieth year. Although it had long been held that the disease might be congenital,[2] this view has of late been abandoned.[3] Extensive chemical, physical and dietary investigations have recently added greatly to our knowledge of the causal factors of the disease (see p. 1075).

The physiological growth of bones presents three phases. They grow in length by the production of bone in the cartilage between the epiphysis and diaphysis; in thickness, by the growth of bone from the inner layers of the periosteum. At the same time the medullary canal is enlarged, in proportion to the growth of the bone, by the disappearance of the inner layers of bone.

In rickets these three phases of growth are abnormal. The cartilaginous and subperiosteal cell growth which precedes ossification, goes on with increased rapidity and exuberance and in an irregular manner, both between the epiphyses and diaphyses and beneath the periosteum, while the actual ossification is imperfect, irregular, or wanting. Even the lime salts of the previously ossified bone may be removed by halisteresis. At the same time the dilatation of the medullary cavity goes on irregularly and often to an excessive degree. The marrow may be replaced by fibrous tissue in which imperfect bone or osteoid tissue may develop. Microscopic examination of the region in a rachitic bone between the epiphysis and diaphysis (Fig. 733), shows that the cartilage cells are not regularly arranged in rows along a definite zone in advance of the line of ossification, as in normal development, but that there is an irregular heaping-up of cartilage cells, sometimes in rows, sometimes not, over an ill-defined and irregular area. The zone of calcification also, instead of being narrow, regular, and sharply defined, is lacking in uniformity. Areas of calcification may be isolated in the region of proliferating cartilage cells, or calcification may be altogether absent over considerable areas.

Corresponding to these irregularities the ossification zone is also irregular. New-formed bone and marrow cavities containing blood-vessels may lie in the midst of the cartilage, or masses of cartilage may lie deep in the region which should be completely ossified. In other places it seems as if the cartilage tissue were directly converted by metaplasia into an ill-formed bone or osteoid tissue. It will readily be seen from this that the medullary spaces of the new-formed bone are irregular, and this abnormality is enhanced by the premature intramedullary absorption.

[1] See *Schmorl*, Deutsch. Arch. f. klin. Med., 1905, lxxxv, 170; and Ergebn. d. inn. Med. u. Kinderheilk., 1909, iv, 403. For general studies of the lesion, see *v. Recklinghausen*, Untersuchungen über Rachitis u. Osteomalacie, Jena, 1910; *Schmorl*, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 248; 1909, xiii, 40; *Schmidt, M. B.*, ibid., 1909, xiii, 3; *Dyrenfurth, F.*, Virchows Arch., 1906, clxxxvi, 321; *Goetsch, W.*, Zieglers Beitr., 1906, xxxix, 218.

[2] *Salvetti, C.*, Zieglers Beitr., 1894, xvi, 29 (bibl.).

[3] *Escher*, Jahrb. f. Kinderheilk., 1902. lvi, 613; *Wieland*, Ergebn. d. inn. Med., 1910, vi, 64.

Similar irregularity in the bone formation may be seen beneath the periosteum. An excessive proliferation of cells in the inner layers of the periosteum, the irregular calcification which occurs about them, and the absence of uniformity in the elaboration of ill-structured bone, conspire to produce an irregular, spongy bone tissue instead of the compact, lamellated tissue which is so necessary here for the solidity of the structure. The increased cell growth between the epiphyses and diaphyses produces the peculiar knobby swellings which are characteristic of rickets. The diseased areas show marked congestion.

The result of these processes is that the bones do not possess solidity and cannot resist the traction of the muscles or outside pressure. The epiphyses may be displaced or bent, especially in the ribs, less frequently in the long bones. The long bones and the pelvic bones may be bent

Fig. 733.—Rachitic Bone.
Showing ossification zone in a longitudinal section of a rib.

into a variety of forms (Fig. 734). Incomplete fractures are not infrequent. Complete fractures do not usually occur until the later stages of the disease, when the bones have become more solid. The head is often square; the cranium may be unnaturally large for the size of the face, due either to edema or to a mild hydrocephalus; the fontanelles and sutures may remain open; the bones may be soft, porous, and hyperemic, while at their edges there may be rough, bony projections beneath the pericranium. Sometimes, especially in the occipital bone, there are rounded defects in the bone, filled only with a fibrous membrane; this constitutes one of the forms of *craniotabes* (Fig. 735). The defects are probably due to the pressure of the edematous brain from within plus the pressure from the weight of the head on the pillow from without.

It does not fall within the scope of this work to describe the various deformities which may occur as a result of this disease. The familiar pigeon breast; the rows of knobs along the sides of the chest from bend-

ing and dilatation of the ribs at the point of junction of cartilage and bone (*rachitic rosary*); the knock-knees, bow-legs, spinal curvatures, etc., may all be the result of rachitic weakening of the bones.

After a time the rachitic process may stop and the bones take on a more normal character. The porous bone and osteoid tissue become compact and even unnaturally dense; the swellings at the epiphyses disappear; many

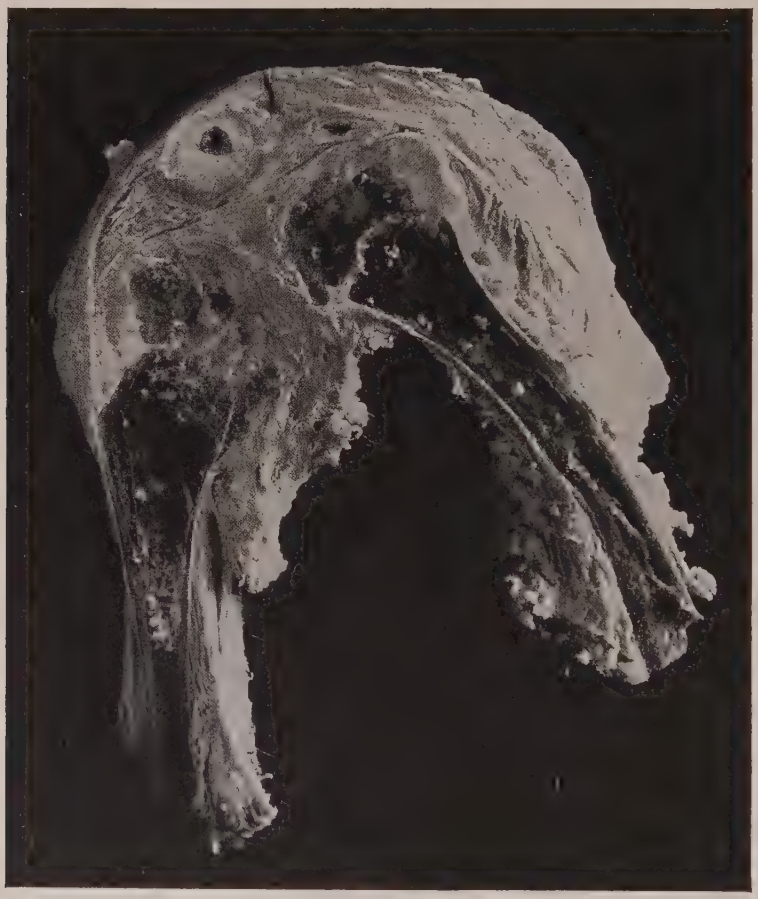


Fig. 734.—Rickets.
Showing irregular ossification and bending of the long bones.

of the deformed bones may become of a normal shape. In severe cases, however, the deformities continue through life; especially there is a cessation of the growth of the bones in their long axis, so that the persons affected are dwarfed.

The disease may have an acute or a chronic character. The acute form begins usually during the first six months of life. The children are apt to suffer from vomiting, diarrhea, profuse sweating, chronic bron-

chitis and pneumonia, general anemia, and wasting. Either they die or the rachitic process is gradually developed. The chronic form is seen in older children, and often in those apparently healthy. The changes in the bones may take place without constitutional symptoms, though there are often catarrhal bronchitis, pneumonia, and anemia, with enlargement of the spleen. Occasionally, the anemia is very severe (von Jaksch type) and may cause death.

It is now generally believed that rickets is due to some perversion of the mineral metabolism. The result of this abnormality is both a deficient and abnormal calcification of the bones. The failure of normal deposition of calcium phosphate in the bones of the child is not due to a fault in the bony tissue itself, but lies rather in the constitution of the blood and lymph which bathes it and furnishes its food. Shipley[1] has found that when a rachitic bone is placed in normal blood serum it at once begins to calcify. In the blood of children suffering from rickets subnormal values are almost always found in the phosphorus or calcium, or in both.

Classifying rickets on a chemical basis, three types may be distinguished.[2] In the first, the calcium content of the serum is normal, but the phosphorus is reduced, producing the so-called low phosphorus rickets, which is the classical type described by Schmorl and others. When the calcium content of the blood is reduced, and the phosphorus remains normal, the child offers a clinical picture resembling true rickets, but the histological changes in the bones differ slightly. Tetany is not infrequent, owing to the low blood calcium. When both calcium and phosphorus are below normal, calcification of the bones is retarded, but the abnormalities differ from those of the two types described above, and while Park is inclined to include it in the group of true rickets, others classify it under the name osteoporosis (see pp. 1081 and 1083).

The study of the etiology of the disease has been much helped by the fact that the albino rats develop rickets with ease, and in these animals the characteristic changes in the bones can be produced in three ways: first, by diminution of the calcium or phosphorus of the food; secondly, by a deficiency diet containing an insufficient quantity of the anti-rachitic vitamin D, and third, rickets can be produced by confining the animals where they get little or no daylight, keeping the diet at the same time low in calcium or phosphorus. The disease can be cured by exposure either to the direct rays of the sun, or to ultraviolet light from a quartz or carbon arc without changing the diet.

Clinically more than one factor usually is active. Not every child develops rickets if kept in dark quarters. Nevertheless rickets is rarely seen in the tropics or among mountainous people where the ultraviolet radiation from the sun is large in amount. The lack of exposure to light may cause rickets secondarily, for such children are apt to be those of the poor who can not afford proper types of food which contain vitamin D

[1] *Shipley*, Johns Hopkins Hosp. Bull., 1924, xxxv, 304.

[2] For fuller information and extensive bibliographies see *Park*, Physiol. Reviews, 1923, iii, 106, and *Sherman*, Chemistry of Food and Nutrition, 3rd edition, New York, 1927.

in abundance, such as codliver oil, or fresh vegetables. The ultraviolet light certainly works indirectly by forming in the skin an as yet not definitely identified compound related to cholesterol or phytosterol. The skin contains considerable amounts of cholesterol, and if this substance is rayed with ultraviolet light it becomes anti-rachitic. It has been suggested that the reason why codliver oil is rendered anti-rachitic is that the organisms that the codfish eat have been exposed to the direct sunlight and hence carry the anti-rachitic substance to the animal. How the anti-rachitic vitamin of codliver oil, or egg yolk, or whole milk, or fresh vegetables, acts beyond the fact that it presumably mobilizes or at least renders more available the calcium and phosphorus of the body, is not known.

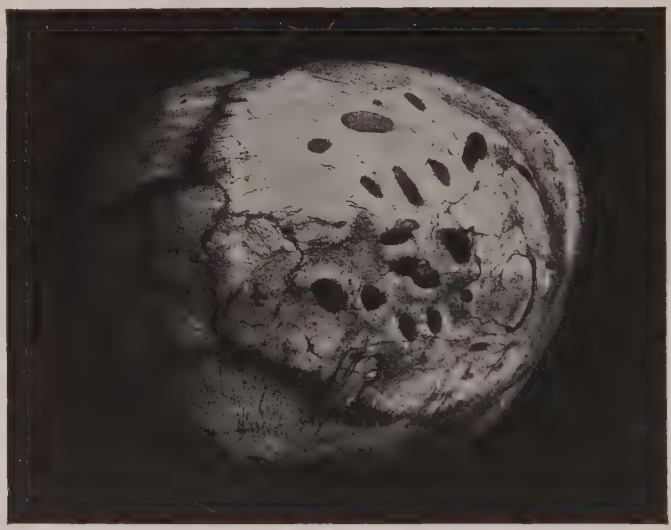


Fig. 735.—Craniotabes.
This skull of a child is large, its bones are thin, with holes due to faulty development and covered only by a thin, fibrous membrane.

Möller-Barlow Disease (Osteotabes Infantum).—This is a disease of infants, occurring usually in the first year of life, and is due apparently to feeding with boiled milk or artificial foods. Clinically and pathologically it resembles the scurvy of adults[1] and like the latter can often be cured by the addition to the diet of fresh fruit juices. The bone changes are the important lesion. The normal cellular marrow is replaced by a loose, poorly vascularized fibrous tissue, with absorption of the bony tissue. The bone ceases to grow while the normal resorptive activities continue, resulting in rarefaction of the bone trabeculæ and imperfect ossification at the epiphyseal junctions. The epiphyses are, in consequence, easily separated from the diaphyses, and the rib cartilages from the ribs. Fracture of the diaphysis is not infrequent. Coincident with these bone changes a hemorrhagic diathesis makes its appearance, and

[1] *Looser, E.*, Jahrb. f. Kinderheilk., 1905, lxii, 743; *Schmorl, G.*, ibid., 1907, lxv, 50.

blood accumulates under the periosteum of the long bones and skull, in the marrow cavity, and, in severe cases, in the skin, mucous membranes, eyelids, orbit, and kidney.[1] The gums may swell, become spongy, and bleed. If the disease is cured under proper feeding, the alterations in the normal osteogenesis and the subperiosteal hemorrhages may lead to permanent deformities and bony overgrowths (see also page 495).

Rickets is present in about half the cases, though the two diseases are of an entirely different nature.[2]

DISTURBANCES OF CIRCULATION.

Hyperemia.—The evidences of this condition are most apparent to the naked eye in the periosteum and marrow, particularly the latter. Hyperemia occurs usually as an accompaniment of inflammatory processes in the bone; when it is marked, the periosteum is swollen and red; the compact bone tissue may appear of a pink color, while the marrow may be of a uniform dark red color or mottled with red and reddish yellow.

Hemorrhage.—This may be due to wounds and injuries and to inflammatory and necrotic processes; hemorrhages often accompany adult and infantile scurvy, purpura, hemorrhagic diathesis, and leukemia. Clots of considerable size between the periosteum and bone may lead to serious consequences by cutting off the blood supply to the superficial layers of bone and thus inducing necrosis. But when not infected through contact with the air or by microorganisms brought in the circulatory channels, they are not usually of serious import, and are readily absorbed, though the periosteum may be stimulated to new and irregular bone formation.

INFLAMMATION.

The periosteum, bone tissue, and marrow are so intimately connected that in most cases they all share to a greater or less degree in the pathological alterations of the bones. But as sometimes one, sometimes another, is most markedly involved, it is convenient to consider separately here the inflammatory changes by which they are respectively affected.

Periostitis.

Exudative inflammation in the periosteum is essentially similar to this form of inflammation in other parts of the body, except as it is modified by the relationships of the connective tissue and blood-vessels to the hard bone and by the presence and performances of the osteoblasts and associated cells peculiar to bone. Several forms are known.

[1] *Heubner, O.*, Berl. klin. Wchnschr., 1903, xi, 285; *Weiss, S.*, Arch. f. Kinderh., 1905, xli, 43; *Fraenkel, E.*, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1904, vii, 62; 1906, x, 1; 1908, xii, 151, Ergänz. Heft, 1911–12, xviii, 172.

[2] *Schmorl, G.*, Zieglers Beitr., 1901, xxx, 215; *Schödel* and *Nauwerck*, Möller-Barlow'sche Krankheit, Jena, 1900.

Simple Exudative Periostitis.—This is apt to occur in children and ill-nourished persons after comparatively slight injuries or from unknown causes. The periosteum is thickened, succulent, congested, and more or less abundantly infiltrated with leucocytes. It becomes less firmly adherent to the bone, and the cells of the inner layers are increased in number. This form of inflammation may terminate in resolution, or it may lead to other phases of inflammation. Even in the mild cases, the irritation often leads to the formation of small nodules or spicules of bone (osteophytes) under the periosteum (see Ossifying Periostitis).

Suppurative Periostitis may begin as a simple or as a purulent inflammation. The pus is formed in the inner layers of the periosteum, and between it and the bone. The outer layers of the periosteum may for a long time resist the suppurative process. The accumulation of pus may dissect up the membrane from the bone and leave the latter bare. The pus thus formed may remain in this position for a long time, or be absorbed, or become dry and cheesy, or it may burst through the periosteum and lead to abscesses in the soft parts. The bone, if separated from its nutrient membrane, may remain unchanged, but more frequently necrosis or inflammation of the bone itself is set up. Such a periostitis may run an acute or a chronic course.

Sometimes suppurative periostitis takes on a very malignant character. Pus is developed not only beneath, but in the periosteum, forming abscesses filled with foul pus. The periosteum breaks down into a gangrenous, foul-smelling mass, and the same change may affect the neighboring soft parts. The medulla may take part in the process and break down into a purulent, gangrenous mass. Hemorrhages may complicate the process. The lymph-nodes may be enlarged and swollen; abscesses may form in different parts of the body; and the patient may die with the symptoms of pyemia. The streptococcus and staphylococcus pyogenes are the most common excitants of suppurative inflammation.

Fibrous Periostitis.—This is a chronic form of inflammation, resulting in the development of new connective tissue in the periosteum, which becomes thickened and dense and usually adherent to the bone. It may accompany necrosis, chronic arthritis, chronic ulcers of adjacent soft parts, etc., or follow simple acute periostitis. It may in many instances be regarded as a conservative process of a reparative character.

Ossifying Periostitis results in the formation of new bone from the inner layers of the periosteum. The masses of new-formed bone, called *osteophytes*, are of variable shape. They may form a thin, velvet-like, villous layer (Fig. 736); or appear as little spicula; or form larger, rounded masses (Fig. 737 and 738), or a thick, uniform layer extending over a large part of a bone. They may have at first a loose, spongy character, and be loosely connected with the old bone. But layers of compact bone tissue are formed within their medullary spaces, which are thus gradually filled, and they join the old bone so that they may finally become as compact as or even more compact and dense than normal bone to which they are firmly joined. The hyperostoses and exostoses thus

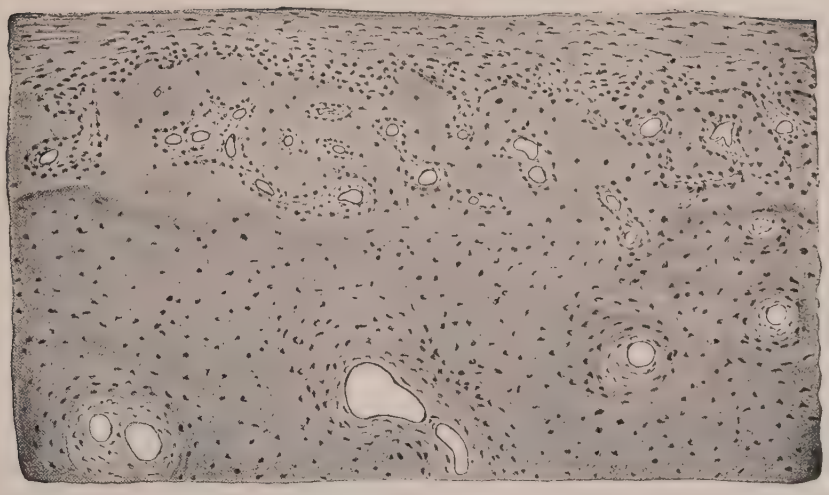


FIG. 736.—OSSIFYING PERIOSTITIS.
An irregular layer of new bone is forming between the periosteum and the old bone.

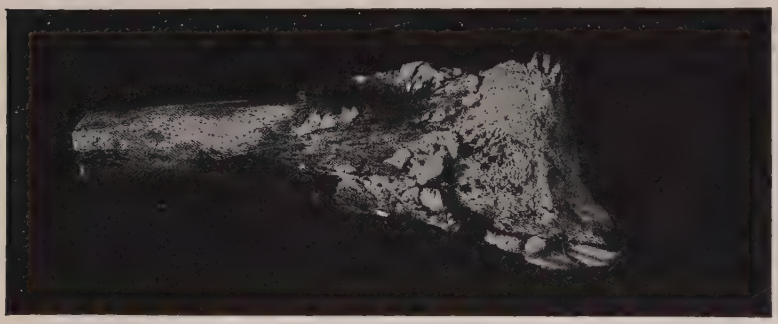


FIG. 737.—OSSIFYING PERIOSTITIS—TIBIA.
Large exostoses at the end of the bone. The process involves the joint, and the bone is enlarged.

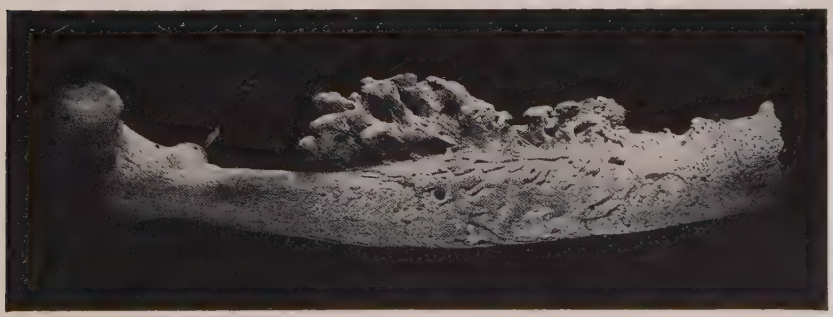


FIG. 738.—OSSIFYING PERIOSTITIS WITH LARGE EXOSTOSES—FEMUR.
A large part of the shaft is thickened and covered with ragged platelets of new-formed bone while above large rough exostoses project. This bone has been the seat of rarefying and formative osteitis.

formed may remain indefinitely, or they may gradually become smaller and finally disappear by absorption.

The formation of new bone in osteophytes, or in dense masses beneath and in the periosteum, occurs as a result of the same process by which bone tissue is normally formed. The osteoblasts, which are developed along the blood-vessels, possess the power of depositing osseous basement substance about themselves and so forming bone. Pathological new formation of bone differs from the normal mainly in the conditions under which it occurs. The blood-vessels around which the pathological bone develops, grow out of the old vessels, as in the formation of granulation tissue, are irregularly arranged, and are subject to a variety of abnormal nutritive and mechanical conditions, so that the new bone is usually formed, not in a series of definite systems of lamellæ, but, as above

Fig. 739.—Tuberculosis of the Joint.
Shows caries with extensive destruction of the bone.

described, in a series of irregular spicula or masses. Moreover, as will be seen further on, the conditions under which it is formed being liable to change, and itself serving no definite purpose in the economy, as does normal bone, pathological new bone is often an evanescent structure. The details of its disappearance will be considered below.

Syphilitic Periostitis.—Syphilitic infection may excite simple, purulent, fibrous, or ossifying periostitis. In addition to these, gummata (page 312) may be developed in the periosteum in long bones, most frequently on the shaft, where they cause a more or less fusiform enlargement. The bone tissue is usually more or less involved. The gummata may be absorbed or undergo cheesy degeneration, or be converted into fibrous tissue, or they may suppurate.

Tuberculous Periostitis.—In badly nourished persons, particularly in children suffering from scrofula, chronic purulent periostitis is frequently

associated with the formation of miliary tubercles. Abscesses are apt to form in and about the periosteum, and when these are evacuated granulation tissue, which contains miliary tubercles, may develop. The bone is apt to be involved to a greater or less extent in simple inflammatory changes or caries (Fig. 739).

Osteitis.

Inflammation in bone tissue is dependent upon the same general conditions and presents essentially the same series of phenomena as inflammation in other kinds of connective tissue. But it is variously modified in detail by the peculiar dense and unyielding character of the basement substance, and by certain peculiarities of the blood supply and the nutritive conditions under which the cells are placed. In simple exudative inflammation the same series of phenomena occurs in connection with the blood-vessels as in other tissues, resulting in the production of serum, fibrin, and pus; but these changes are limited in extent, and they are constantly associated with striking alterations in the basement substance. It is these secondary alterations in the basement substance which lend to inflammations of the bone their most essential characters, and in the prominence which these assume the fundamental alterations are often overlooked. The most common of these secondary alterations are the absorption of the hard basement substance of the bone and its replacement by, or conversion into, young cellular forms of fibrillar connective tissue or marrow tissue, and the formation, in a more or less typical manner, of new bone. The active phenomena of inflammation in bone are processes of the blood-vessels and the fibrillar connective tissue as in other parts of the body, the hard bone substance being in a certain sense only secondarily involved.

As a result of these changes the bone in simple inflammation becomes more vascular, and, with an increase of spaces filled with granulation or marrow tissue, more porous at the expense of the dense basement substance; or the new-formed spaces or the marrow cavities may be constantly encroached upon by the new-formed bone lamellæ on their walls, so that the bone becomes more compact; or as is frequently the case, both series of changes occur either simultaneously in different regions, or follow each other, or are variously associated together. Very frequently one or the other of the opposing forms of alteration predominates, or one may occur to the exclusion of the other, and we thus have two prominent forms of inflammation, which are called *rarefying osteitis* or *osteoporosis*, and *condensing osteitis* or *osteosclerosis*. The exact nature of the conditions under which in one case the bones become more, in another less dense, we do not understand. Nor is the exact way in which the osteoclasts dissolve hard bone, or the osteoblasts secure and deposit inorganic salts and become bone cells as yet clear. Furthermore, more or less characteristic forms of inflammation may occur in syphilitic and tuberculous infection—*syphilitic* and *tuberculous osteitis*. Suppurative osteitis may further complicate the process.

In addition to these phases of inflammation in bone, and in frequent and varied association with them, there are alterations leading to death and destruction of bone tissue in greater or less amount, which are called *caries* and *necrosis*. Finally, any of these forms, and commonly several of them at once, are variously associated with more or less marked inflammatory or degenerative alterations of the periosteum on the one hand, of the marrow tissue on the other, or of both combined.

Rarefying Osteitis consists essentially in the formation in the marrow spaces, or Haversian canals, or beneath the periosteum, of new, very cellular and vascular tissue, resembling granulation or young marrow tissue, under whose influence the basement substance of the bone is absorbed. This absorption of the bone takes place largely as bone is absorbed in normal growth, namely under the influence of certain large cells, which are grouped around the blood-vessels. If a thin section of bone which

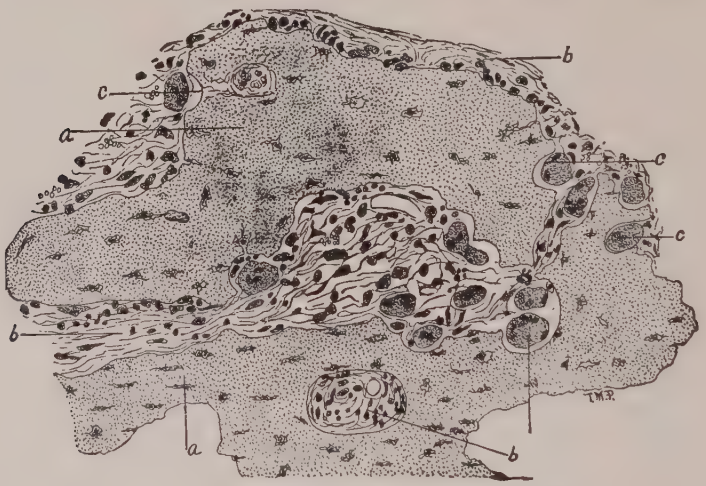


Fig. 740.—Rarefying Osteitis in Ulna of Child.
a, Isolated bone fragment with rough edges; *b*, marrow tissue; *c*, Howship's lacunæ with osteoclast.

is undergoing absorption be examined (Fig. 740), the edges of the bone which border on the vascular surfaces are found irregularly indented by deep or shallow depressions, sometimes simple, sometimes quite complex. These are called *Howship's lacunæ* and are usually filled or lined by larger and smaller granular, frequently multinuclear cells—the so-called *osteoclasts*. In the larger lacunæ there may be granulation tissue with loops of blood-vessels, with or without osteoclasts. Under the influence of the osteoclasts or of the new vascular tissue, the bone is gradually absorbed.

On the other hand, there may be irregular branching channels through the bone across the lamellæ, which appear to be due to the enlargement and coalescence of the lacunæ and canaliculi, without the direct influence of blood-vessels or other cells than the fixed cells of the bone. The tissue which replaces the absorbed bone may be very rich in small spheroidal cells, or it may be more or less fibrillar.

As a result of this process irregular islets of bone tissue may be entirely separated from adjacent bone and surrounded by a more or less fibrillar vascular tissue; this is most apt to occur in the cancellous tissue. Or the originally compact bone may become traversed by a series of larger and smaller, irregularly branching, communicating channels with ragged walls. These progressive alterations may cease, and be succeeded by a new formation of bone along the edges of the channels or cavities.

Rarefying osteitis may occur as an independent process from unknown causes; it is often associated with syphilis, with diseases of the joints, with fractures or other injuries to the bone; it often forms a predominant feature in tuberculous inflammation of the bones. It is chiefly by a rarefying osteitis that bone tissue is eroded and destroyed in the vicinity of tumors, aneurysms, etc., which exert pressure on the bones. By the same process the sharp ends of fractured bones may be rounded off as healing proceeds.

When this form of inflammation occurs in cancellous bone tissue the marrow is red or gelatinous, and the bony septa may disappear altogether, so that in extreme cases there may be, instead of cancellous bone, a mass of granulation tissue. When the process occurs in the articular extremity of a bone the granulating medulla may send little offshoots through the articular cartilage. These may become fused together and inflammation of the joint may follow. The walls of the shafts of the long bones may be converted into spongy tissue. If, as is sometimes the case, an ossifying periostitis occurs at the same time, the bone is thickened but spongy; or sometimes there are concentric layers of compact bone tissue, separated by rarefied bone.

Condensing Osteitis (Osteosclerosis).—This lesion is characterized by the new formation of bone in the walls of the marrow cavities or Haversian canals. The bone is formed under the influence of the blood-vessels and osteoblasts, as in normal bone formation, but with less regularity. It may result in the conversion of cancellous tissue into compact bone, in the filling up of the medullary cavity of long bones with more or less dense bone tissue. The compact bone, owing to the filling of its Haversian canals, may become very dense and ivory-like. When the medullary cavities of long bones are involved the yellow marrow is converted into red marrow by the absorption of fat and by increased vascularity. This change is due, in part at least, to the condensation, so to speak, into definite areas, of the marrow tissue invisible in the fat, and also to the destruction of the marrow in other areas, as a result of which functional hyperplasia of the remaining marrow occurs. Severe and even fatal anemia may result if the osteosclerosis is extensive, and a secondary osteosclerosis may in rare instances follow the development of a leukemia or a severe anemia.[1]

Osteosclerosis is frequently associated with ossifying periostitis. It often follows rarefying osteitis, and then the Howship's lacunæ resulting from the original absorption process may be filled and covered in with new bone lamellæ (Fig. 741). The presence in the bone-marrow of cer-

[1] *Assmann, H.*, Zieglers Beitr., 1907, xli, 565 (bibl.).

tain types of metastatic carcinoma, especially prostatic, may lead to an extensive osteosclerosis.[1] It is apt to occur in connection with necrosis or chronic inflammation of adjacent soft parts, and is then a reparative and conservative process, but it sometimes occurs independently under unknown conditions.

Suppurative Osteitis (Abscess of Bone).—This process occurs usually in the ends of the long bones, and is associated with rarefying osteitis. As the bone tissue is absorbed, a circumscribed cavity may be formed in the bone, filled with pus, and lined with granulation tissue.

Less frequently abscesses are formed in the shaft of a long bone by circumscribed suppuration of the medulla. Such abscesses may occur in old people and may be of long duration. They may gradually enlarge

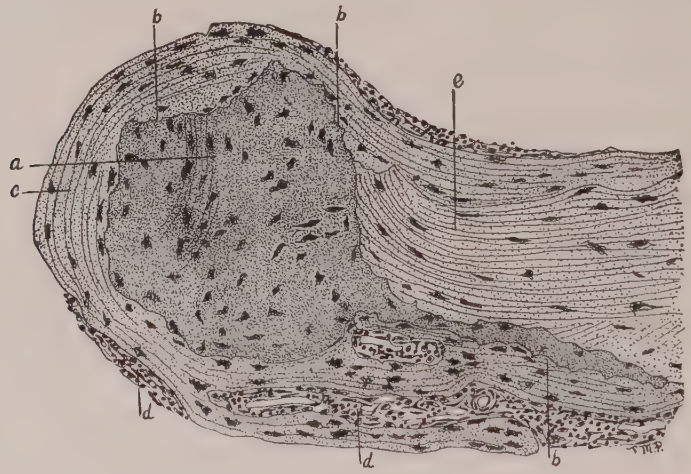


Fig. 741.—Condensing Osteitis, or Osteosclerosis, in Ulna of Child
a, Fragment of old bone with roughened, sinuous edges; *b*, old Howship's lacunæ covered with more recently formed bone lamellæ; *c*, *d*, new Haversian canals.

and be accompanied by an ossifying periostitis, so that the bone is expanded. The abscesses in suppurative osteitis sometimes develop rapidly and may perforate. On the other hand, instead of abscesses, there may be a diffuse infiltration with pus of the Haversian canals or of the spaces formed by rarefying osteitis (see Osteomyelitis, below). Staphylococcus aureus is usually found in the pus.

The lesion of phosphorus poisoning is of this type. It begins with a productive osteitis and periostitis which, by infection from the mouth becomes a suppurative process involving both the periosteum and the bone.

Osteomyelitis.—The tissues of the medulla so frequently share in the inflammatory processes in bone that many conditions described as osteitis are really osteomyelitis. It is customary, however, to reserve the latter name for those cases in which the medulla is primarily or chiefly involved.

[1] *v. Recklinghausen*, Festschrift f. Virchow, Berlin, 1891.

Acute Infectious Osteomyelitis.—This may occur as the result of a local injury which permits the access, or favors the development, of pyogenic microorganisms; it may be metastatic, resulting from the transportation of infectious material from other parts of the body in septicemia and pyemia, in typhoid fever, in the exanthematous fevers, and under other conditions; or it may occur without evidence of local predisposition or of infectious processes in other parts of the body.

The lesions of acute infectious osteomyelitis are, in the large majority of cases at least, due to the presence and action of the pyogenic cocci, the Staphylococcus pyogenes and the Streptococcus pyogenes, and in many of its forms it may be regarded as one of the phases of septicemia or septicopyemia.

While the lesions vary widely, the following general description is applicable to a considerable proportion of the cases:

At the commencement of the disease, which usually begins in the shaft of one of the long bones, there are hyperemia and edema of the medulla, so that on inspection the marrow is found to be soft and of a dark red color. A diffuse suppuration now rapidly ensues, and the marrow becomes streaked or mottled with gray. Occasionally, though not often, larger and smaller abscesses may form in the marrow. The inflammatory areas may be circumscribed; or, in the more malignant cases, the entire marrow may become rapidly involved. The cancellous tissue of one or both of the epiphyses usually becomes affected. The disease, however, is not commonly confined to the medullary spaces. The periosteum becomes edematous and infiltrated with pus, and the surrounding soft parts may become the seat of intense inflammatory changes. Abscesses of the periosteum or surrounding tissues are apt to form. As a result of these changes, necrosis of greater or less portions of the bone may ensue with the formation of larger or smaller sequestra (see p. 1089). The medullary cavity may become enlarged as pus accumulates, and the wall of the bone may be broken through, permitting the discharge of pus outward. Sometimes several bones are involved at once. Secondary involvement of the joints is very frequent. Here there may be only a serous or purulent exudation; or the acute and destructive inflammatory process may extend beneath the joint and produce extensive alterations. In young persons the epiphyses very frequently become separated from the shaft by the destruction of the cartilage which binds them together.

In the severer cases, which are often called, *par excellence*, malignant osteomyelitis, the changes may be very rapid and destructive. The medulla is disintegrated and gangrenous; the joints are soon involved; necrosis of large portions of the bone, sometimes of the whole shaft, occurs, the periosteum and surrounding parts become gangrenous; the veins contain thrombi, and pyemic infarctions and abscesses may form in various parts of the body.[1]

[1] Consult, for an elaborate treatment of acute osteomyelitis in its relationship to other forms of inflammation, with bibl., *Jordan*, Beitr. z. klin. Chir. (Bruns), 1893, x, 587. For a study of this condition in childhood, see *Koplik* and *Van Arsdale*, Am. Jour. Med. Sc., 1892, ciii, 422 and 535.

Chronic Osteomyelitis.—In prolonged cases of osteomyelitis there is apt to be more or less ossifying periostitis and osteosclerosis, and fistulæ may form in the bone, through which the exudates are discharged.[1]

Tuberculous Osteitis is primarily a tuberculous inflammation of the soft parts of bone with associated rarefying and formative processes in the hard bone. The tubercles are sometimes small and scattered (Fig. 742), sometimes they unite to form larger foci or large diffuse caseous masses. There may be extensive involvement of the medulla. Rarefying and condensing osteitis and necrosis often accompany the tuberculous process. Thus the bone frequently becomes spongy or fragile

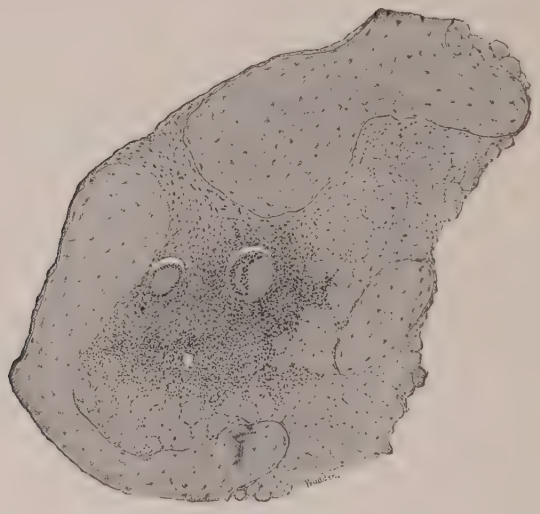


Fig. 742.—Tuberculous Osteitis.
A miliary tubercle formed in the cancellous tissue near the joint in tuberculous arthritis.

(Fig. 739). Much of the new tissue formed in tuberculosis of the bones is simple granulation tissue or fibrous tissue of reparative character.[2]

Not infrequently an exudative inflammation occurs, with the formation of the so-called cold abscesses. This abscess formation in bone as well as in soft parts may be due to the tubercle bacillus alone. But concurrent infection of tuberculous areas often takes place, the pyogenic or other organisms gaining access to the involved region either through the blood-channels or by surface openings, fistulæ, sinuses, etc.

Tuberculous inflammation is most frequent in early life and, save for the smaller bones, such as the phalanges, metacarpal, metatarsal, it rarely involves the shafts of bones.[3] In young children, however, the disease involves the phalanges of the hands and feet in the form of spindle-

[1] For a résumé of the deformities resulting from osteomyelitis, consult *Park, R.*, Med. Record, 1895, xlviii, 613.

[2] For a review of recent opinions on bone tuberculosis, see *Fraser, J.*, Jour. Am. Med. Assn., 1915, lxiv, 17.

[3] For a study of the relative prevalence of human and bovine types of tubercle bacilli in bone and joint tuberculosis of children, see *Fraser, J.*, Jour. Exper. Med., 1912, xvi, 432 (bibl.); *Griffith, A. S.*, Jour. Path. and Bacteriol., 1916, xxi, 54; and *Cobbett*, The Causes of Tuberculosis, Cambridge, 1917.

shaped swellings (*spina ventosa*). This is produced by deposition of new bone by the periosteum while the central spongy portion is progressively absorbed. A similar type is sometimes seen in the ulna and tibia. It is often associated with tuberculous involvement of the joints (Fig. 739). The bovine type of bacillus is present in about one-fourth of the cases.

Syphilitic Osteitis.—*Syphilitic infection* may lead to one or other of the forms of osteitis just described, or gummatous nodules may form. Syphilitic osteitis usually commences in the periosteum, which becomes thickened and infiltrated with cells, so that there may be a circumscribed thickening of the periosteum, with or without distinct gummata. The vessels which extend from the periosteum into the bone become surrounded by new cellular tissue, which causes an enlargement of the canals. At this stage, if the periosteum be stripped off, it drags with it the vessels surrounded by the new cell growth, leaving the bone beneath with numerous small perforations extending inward. As the disease progresses the channels in the bone enlarge by a rarefying osteitis and coalesce, forming large, irregular defects filled with new fibrous tissue (Fig. 743). In these masses of new tissue, cheesy degeneration may occur, so that the new growth has more or less of the character of a gumma. In the vicinity of these gumma-filled spaces a condensing osteitis may occur, both in the substance of the bone and on the surface, in the form of osteophytes, so that the opening in the bone may be surrounded by an elevated, irregular ring of bone tissue. All this may occur beneath the uninvolved skin, or the skin may participate by a suppurative inflammation, resulting in ulceration. These processes may be circumscribed or involve a large part of a bone. It is not infrequently associated with necrosis of larger and smaller portions of bone. The syphilitic tissue may be absorbed and its place be more or less filled with fibrous tissue. Syphilitic osteitis is most frequent in the cranial bones, but may occur elsewhere, as in the sternum, clavicle, tibia and fibula, the ribs, etc.

Fig. 743.—Syphilitic Osteitis and Periostitis of Ulna.

Congenital Syphilis.—The bones of young children in this condition may show increased density or evidences of periostitis, or irregular thickenings, particularly of the skull. Characteristic lesions are frequently found in the long bones in still-born or young children who are the victims of hereditary syphilis. These lesions are found for the most part

along the border zone between the epiphysis and diaphysis. In normal ossification of the long bones, the border line between the calcification and ossification zones is narrow, sharply defined, and straight, or lightly and evenly curved. In syphilitic bones, on the contrary, this line is broader and uneven, and presents various modifications, which merge into one another, so that all intermediate forms may be seen. In a lesion of moderate grade there may be, between the cartilage and the new-formed spongy bone, a white or reddish-white zone, about two millimeters in breadth, with very irregular borders, consisting of calcified cartilage, in which the linear groups of cartilage cells are more abundant than normal. In more pronounced lesions the calcified zone, still containing an unusual number of cartilage cells, is broader and still more irregular and less sharply outlined against the ossification zone. The cartilage just beyond it is softer and almost gelatinous, and may contain numerous blood-vessels, or islets of connective tissue, of calcification, or of irregular ossification. Finally the bone may be pouched out at the sides around the ossification and calcification zones, and the perichondrium and periosteum thickened. The whitish, irregular, calcified zone is hard and friable. Between this and the new-formed bone there is an irregular, soft, gray or grayish yellow zone, from two to four millimeters in thickness, which forms a loose, readily separated connection between the cartilage and the diaphysis. The white, friable zone consists mainly of irregular rows of degenerated and distorted cartilage cells lying in a calcified basement substance, of irregular masses of atypical bone tissue, and of blood-vessels surrounded by variously shaped cells. The soft zone consists of more or less vascular tissue with homogeneous basement substance, and round and spindle-shaped cells. This soft zone is not sharply outlined against the adjoining new-formed spongy bone, which, instead of consisting of the normal marrow spaces with bony lamellæ between them, is largely composed of granulation tissue.

Different phases of this faulty development may be seen in different bones in the same individual. According to Wegner the lesion is usually most advanced in the lower end of the femur, then in the lower ends of the leg bones and of the forearm, then in the upper ends of the tibia, femur, and fibula.

Not infrequently there is fatty degeneration of the marrow cells and blood-vessels, giving the marrow a reddish yellow color. These alterations of the bones may occur, not only in children who have gummata in other parts of the body, but also in those in whom other evidences of syphilitic infection are absent. So uniform is their occurrence that their presence alone suffices for the establishment of a diagnosis.

NECROSIS.

Necrosis is the death of a larger or smaller portion of bone. This may be induced by conditions which deprive the bone of its proper vascular supply from the periosteum and medulla. It may be associated with suppurative periostitis, osteomyelitis, and osteitis, traumatic sepa-

ration of the periosteum, ulcers of neighboring soft parts, emboli, the action of phosphorus vapor, and exhaustive infectious diseases. Necrosis is a pure form of gangrene, differing from gangrene of soft parts in that the dead bone has at first, and may retain for a long time, the general outward characters of the normal bone; while in dead soft parts rapid absorption may occur, or, should bacteria of various forms be present or gain access to the dead tissue, putrefaction, with complex changes, may ensue.

When a portion of bone has died, inflammation occurs at the dividing-line between the dead and living bone. This inflammation has the characters of a rarefying osteitis (see above), and finally separates the dead from the living bone. The dead bone, or *sequestrum*, may remain smooth and unaltered (Fig. 744), or it may be eroded by the influence of surrounding pus or granulation tissue or osteoclasts. In this way it is possible for the sequestrum, if it be small, to be entirely absorbed. More frequently there is a production of new bone around the sequestrum,

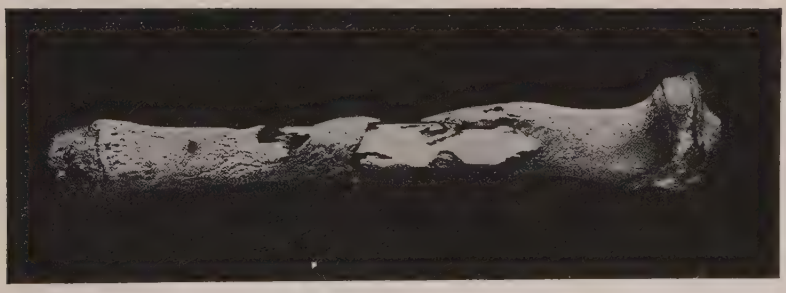


Fig. 744.—Necrosis of Bone.
Showing sequestrum of dead bone partially surrounded by new-formed subperiosteal bone, with thickening of the shaft.

either beneath the periosteum or in the substance of the bone, and this becomes lined with granulation tissue, from which pus may continue to be formed, bathing the sequestrum.

Necrosis may involve the superficial layers, or the entire thickness of the wall of a long bone, or only the spongy tissue and inner layers, or an entire bone, or a number of different portions of the same bone; but it is most apt to occur in compact bone.

The death and separation of the bone may be soon followed by the growth of new bone to repair the loss. The periosteum, the medulla, and the surrounding soft tissues may all take part in this new growth. The new bone is usually irregular, rough, and perforated with openings through which pus formed around the sequestrum may be discharged. If the sequestrum be removed, healing may occur by the formation of new bone; but the bone is usually more or less distorted by the irregular new ossification. Bacteria persist for a long time in sequestra, and are responsible for the acute inflammatory processes sometimes seen after aseptic operations on diseased bones.[1]

[1] *Taylor* and *Davies*, Ann. Surg., 1917, lxvi, 522.

Phosphorus Necrosis.—Under the influence of phosphorus vapor, periostitis and osteitis, particularly of the jaw, are apt to occur, and usually lead to more or less extensive necrosis, generally associated with prolonged and often extensive suppuration.

CARIES.

Caries of bone is essentially an *ulcerative osteitis* resulting in progressive molecular destruction of the bone tissue. It differs from necrosis in that, in the latter larger and smaller masses of bone die, while in caries the destruction is molecular and gradual (Fig. 745). It may occur in connection with any form of osteitis, with periostitis and osteomyelitis, or it may be secondary to inflammatory or destructive processes in the joints or adjacent soft parts. The depressed surfaces of bones in which caries is progressing are rough and more or less finely jagged, and may be covered with granulations. The minute changes by which ulceration and destruction of the bone are produced in caries are somewhat analogous with those in rarefying osteitis, but there are marked degenerative changes in the bone cells, which may become fatty or converted into a granular material. Moreover, the basement substance of the bone, instead of being absorbed, may disintegrate, with the formation of larger and smaller masses of detritus. Sometimes the lime salts are removed from the basement substance, which is converted into atypical fibrillar tissue and fatty and granular detritus. Very extensive suppurations and necrosis may be associated with caries.

Fig. 745.—Caries of the Vertebræ.

Long-continued caries, especially in badly nourished individuals, is apt to become complicated with tuberculous inflammation.

There is very little tendency to spontaneous healing in caries, but it may occur, and the defects produced may be more or less supplied by means of new-formed bone.

HEALING OF WOUNDS AND FRACTURES OF BONE.

The process of healing in bone after fracture is, when uncomplicated, at first similar to that in ordinary healing in fibrous tissue. The blood and other exudates and the tissue detritus are gradually absorbed or disposed of by phagocytes. By a proliferation of connective-tissue cells of the region a larger or smaller mass of granulation tissue is formed. This granulation tissue does not at first differ in appearance from similar tissue formed elsewhere in the body in the reparative phase of exudative inflammation.

But soon, under the influence of the especially endowed cells of cartilage or bone or periosteum, but especially of the last, the granulation tissue becomes partially replaced either by cartilage or by a substance resembling bone in general appearance but containing no lime salts. This is called *osteoid* tissue. These new cartilaginous and osteoid tissues, which are apt to occur together, form irregular masses or interlacing trabeculæ in the stroma of granulation tissue. This constitutes the so-called callus of a uniting fracture (Fig. 746).

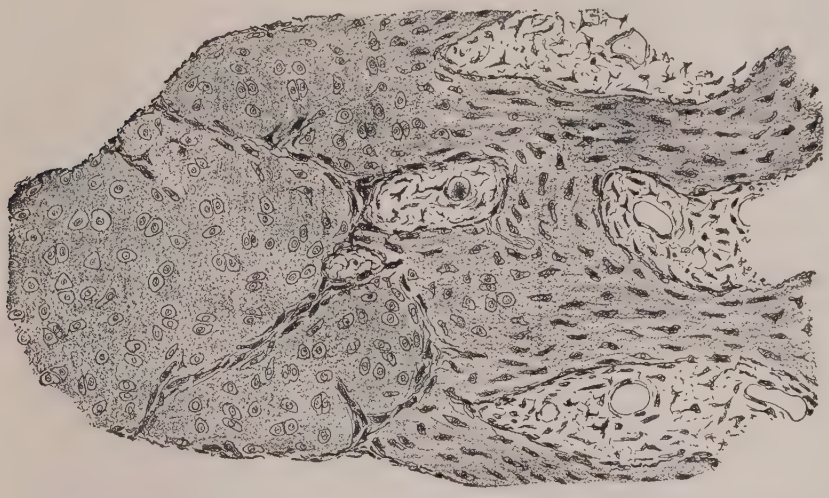


FIG. 746.—NEW-FORMED CARTILAGE AND OSTEOID TISSUE FROM CALLUS AFTER FRACTURE OF THE FEMUR.

Gradually the osteoid tissue becomes osseous, and the masses of cartilage and bands of periosteal and other fibrous tissue, under transformations practically identical with those seen in normal development, are converted into bone. Thus by gradual absorption and re-formation of bone in the usually redundant provisional bony mass, and by the readjustment of its vascular channels, the healing, with more or less permanent deformity, is accomplished (Fig. 747).

If the conditions are not favorable, the healing of fractures may occur only by fibrous-tissue formation, so that so-called "false joints" may

result (Fig. 748). The healing of other injuries and losses of substance occurs by a process similar to that described.

Fig. 747.—Healed Bone after Fracture.
Shows redundant hard bone about seat of fracture.

ALTERATIONS OF THE BONE-MARROW IN LEUKEMIA AND ANEMIA.

In some cases of acute leukemia there is but little change in the bone-marrow, but in the chronic forms, especially when of long duration, there may be great alterations in this blood-producing organ. The change most often seen is a more or less complete replacement of the fatty marrow in the shafts of the long bones by the accumulation, in lymphatic leukemia, of lymphocytes of various types, and, in the myelogenous form, of myelocytes of all varieties. In addition, the marrow contains large numbers of nucleated red cells, phagocytic cells often containing red cells,

Fig. 748.—Ununited Fracture of Radius with Healed Fracture of Ulna after Insertion of a Metal Plate.
The pressure atrophy of the bone is well shown about the screw on the left of the cut.

and not infrequently considerable numbers of small octahedral crystals (Charcot's crystals). All these types of cells are apt to be arranged in foci; that is, there may be a small area composed chiefly of nucleated red cells, another area of myelocytes, and so on.

The degree to which this accumulation of cells occurs varies much in different cases, and the gross appearances of the marrow are consequently very diverse. In some cases the marrow is soft and has a uniform red

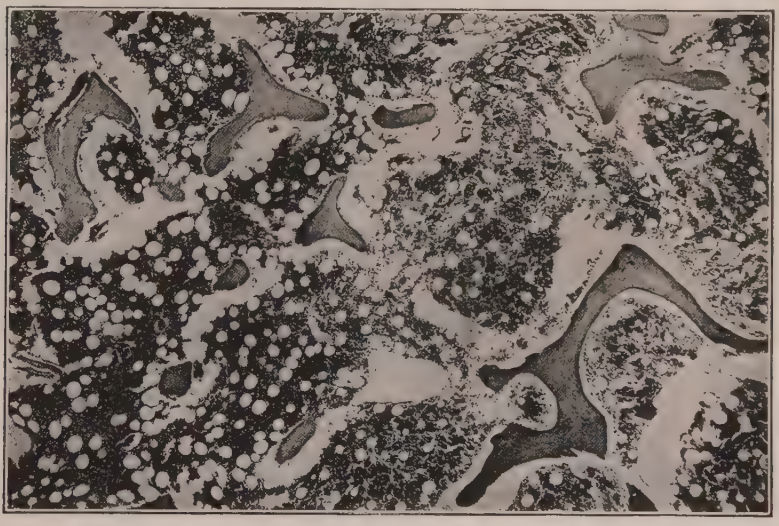


Fig. 749.—Hyperplastic Bone-marrow of Rib.
From a case of purpura hæmorrhagica.

appearance, or it is variously mottled with gray and red. Occasionally circumscribed hemorrhages are seen. In another class of cases, in which the cell accumulation is more excessive, the marrow may be gray, grayish yellow, or puriform in appearance (Fig. 749).

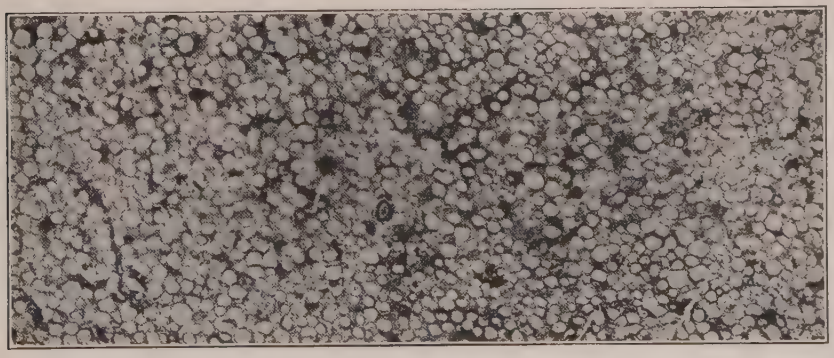


Fig. 750.—Normal Bone-marrow from Shaft of Femur.
The marrow shows little but fat tissue with occasional darker patches containing a few red cells, often nucleated, some leucocytes, and a few of the characteristic megalokaryocytes of the marrow.

These changes may occur in the central marrow cavity, as well as in the marrow spaces of the spongy bone. They may be present in several

or many of the bones. They are usually accompanied by analogous changes in the spleen and lymph-nodes.

In certain cases of acute and chronic *anemia*, particularly in the pernicious and progressive varieties, the marrow, especially of the larger long bones, may lose its yellow color from absorption of the fat, and become red. Microscopical examination of the marrow under these conditions may show myelocytes and sometimes an abundance of developing nucleated red blood-cells and Charcot's crystals.

In many of the acute infectious diseases, typhus fever and typhoid fever, ulcerative endocarditis, recurrent fever, etc., the bone-marrow has been found to be hyperemic, and to contain an excess of myelocytes.

All these lesions of the marrow, although our knowledge of them is still very incomplete, together with what is known of the physiological functions of the marrow, point to a close relationship between the marrow and the spleen and lymph-nodes as blood-producing organs.

Closely related to the leukemias are two forms of tumors of bone arising in the bone-marrow—*chloroma* and *myeloma*.

Chloroma.—Under the name chloroma is grouped a series of tumors which are closely related to the leukemias on the one hand and to the myelomata on the other They are distinguished from the latter by the greenish color which they possess and by the fact that they occur in children and young individuals, while myeloma is a disease of adult life. The tumor masses most frequently involve the bones of the skull, the orbit, and nearby regions, but occur also in the loose connective tissue along the spinal column, and secondarily involve the lymphatic tissue, lymph-nodes, muscles, and thymus, as well as the bone-marrow. In some instances diffuse infiltration of the internal organs also occurs.[1]

Microscopically, two types of chloroma can be distinguished, one composed of lymphocytes, the other composed of myelocytes. The lymph-nodes of the body are more often extensively involved in the first than in the second form, in which the invasion is apt to be diffuse and the bone-marrow especially is involved.

While the green color of the tumor is important in the differential diagnosis between chloroma and myeloma, it is not constant, and may be present in some of the tumors and not in others in the same case. A similar greenish tone may be found in typical leukemia in the masses in the bone-marrow and also very rarely in chronic lymph-node tuberculosis. Bence-Jones' albumose has been found in the urine of cases of chloroma of the myelocytic type.

Myeloma.—Under this name is included a peculiar group of tumors, which, while they resemble the sarcomata in many respects, are distinct from them in their histogenic relationships; that is, they are derived from the special cells of the bone-marrow, and not from the periosteum. These tumors are usually multiple, appearing simultaneously in many parts of the bony structures.[2] They form grayish or reddish masses in the spongy

[1] See page 546 for bibliography and further details.

[2] *Wright*, Trans. Assn. Am. Phys., 1900, xv, 137; *Christian, H. A.*, Jour. Exper. Med., 1907, ix, 325; and *Vance, B. M.*, Am. Jour. Med. Sc., 1916, clii, 693 (bibl.); *Symmers, D.*, Multiple myelomas and their ability to metastasize, Ann. Surg., 1918, lxvii, 687.

bone or in the medullary canal and as they grow excite active resorption of the bone. Spontaneous fractures are frequent and bending of the bone from loss of lime salts is occasionally seen. Metastases in other organs are rare.[1] Another interesting point is the presence in the urine in many of these cases of a peculiar protein called Bence-Jones' albumose, which coagulates on heating and dissolves on further heating in the boiling liquid, only to reappear again as it cools. This protein is not absolutely characteristic of myeloma as it has been found also in some of the leukemias and in isolated instances in chloroma, myxedema, chondrosarcoma, and osteomalacia.

Microscopically, the tumors are composed of four varieties of cells: myelocytes or myeloblasts, lymphocytes, red cells, and plasma cells. In the first type of tumor, which may very well be designated *myelocytoma* (Fig. 751), the cells are large, with oval or irregular nuclei, and many of

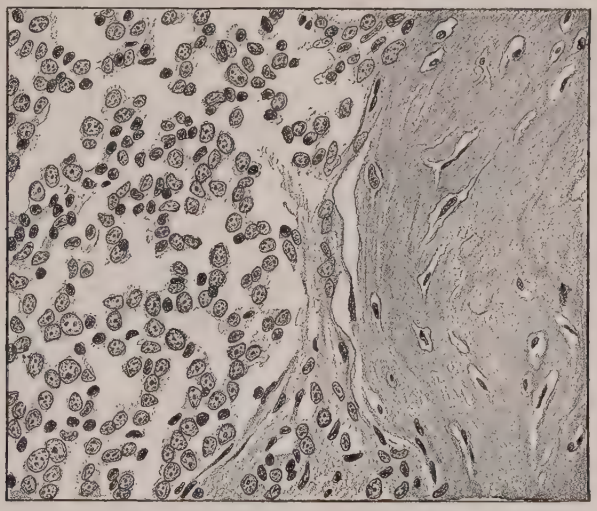


Fig. 751.—Myeloma, Myeloblastic Type.

them show characteristic granulations of the neutrophile myelocytes and give the oxidase tests. Giant cells may be present in small numbers. Tumors formed largely of red cells (*erythrocytoma* or *erythroblastoma*) are extremely rare,[2] while new growths composed largely of plasma cells are the most frequent variety.

TUMORS.

The tumors of bone all belong to the connective-tissue group, arising as they do from either the periosteum, bone-marrow, or cartilage. They may involve either the periosteum, or the compact bone, or the medulla, or, as is more frequently the case, two or more of these structures may be involved at once. Tumors of the bone are usually accompanied by vari-

[1] *Pepper, O. H. P.*, and *Pearce, R. M.*, Jour. Med. Research, 1917, N. S. xxxii, 171 (bibl.).

[2] *Norris, C.*, Proc. New York Path. Soc., 1906, vi, 128; *Ribbert*, Centralbl. f. allg. Path., 1904, xv, 337.

ous secondary and sometimes very marked alterations of the bone tissue, osteoporosis, osteosclerosis, ossifying periostitis, etc. The new growths are very apt to undergo calcification and ossification. Many are dependent for their origin upon anomalies in the development of the skeleton or follow diseases of the bone, such as Paget's disease, osteitis fibrosa, and similar conditions. A traumatic origin has been suggested for many of the osseous tumors, but in a large proportion of instances it has been found on careful study of the lesion that the tumor has antedated the injury. This is especially true of fractures following the slow-growing and relatively benign medullary giant-cell sarcomata.

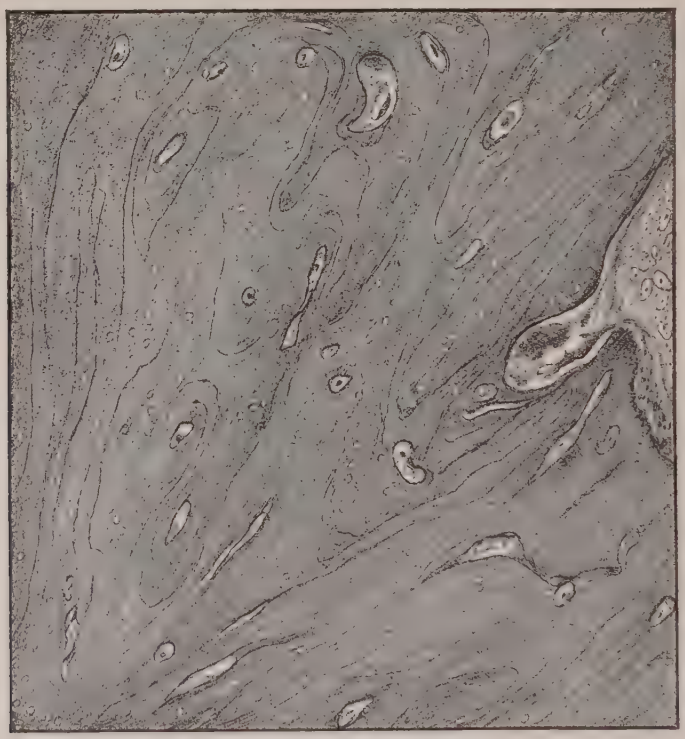


Fig. 752.—Osteoma of Humerus.
Eburnated type.

Fibromata may grow from either the periosteum or the medulla. Their most common seat is in the periosteum of the bones of the head and face. They are apt to form polypoid tumors projecting into the posterior nares, pharynx, mouth, and antrum of Highmore. Central fibromata, *i.e.*, those growing from the medulla, are rare. They usually occur in the lower jaw, but have been found in the ends of the long bones, the phalanges of the fingers, and the vertebræ. Many of the fibromata arising in the lower jaw are merely granulation tissue masses whose vascularity has diminished as the tumor has aged, leaving a firm fibrous mass filling a tooth socket. Such fibromata can hardly be considered

as true tumors, but they comprise a portion of the group of neoplasms known as *epulides*. The fibromata may calcify or ossify, contain cysts, and not infrequently occur in combination with sarcoma.

Myxomata are of occasional occurrence in bone, while myxosarcomata are fairly frequent.

Osteomata.—New formations of bone as a result of inflammatory processes are, as we have already seen, of frequent occurrence in bone, and although not, strictly speaking, tumors, some of their forms are very closely allied to them, and they may therefore be conveniently mentioned here. New growths of bone which arise from the surfaces are called *exostoses* (see Fig. 738) or *enostoses*, according to their origin from the external surface or from the interior of the bone. They may contain all the constituents of normal bone: bone, medulla, vessels, periosteum, and cartilage. The new bone may be compact (Fig. 752) and like ivory, or spongy (Fig. 753), or contain large cavities filled with marrow.

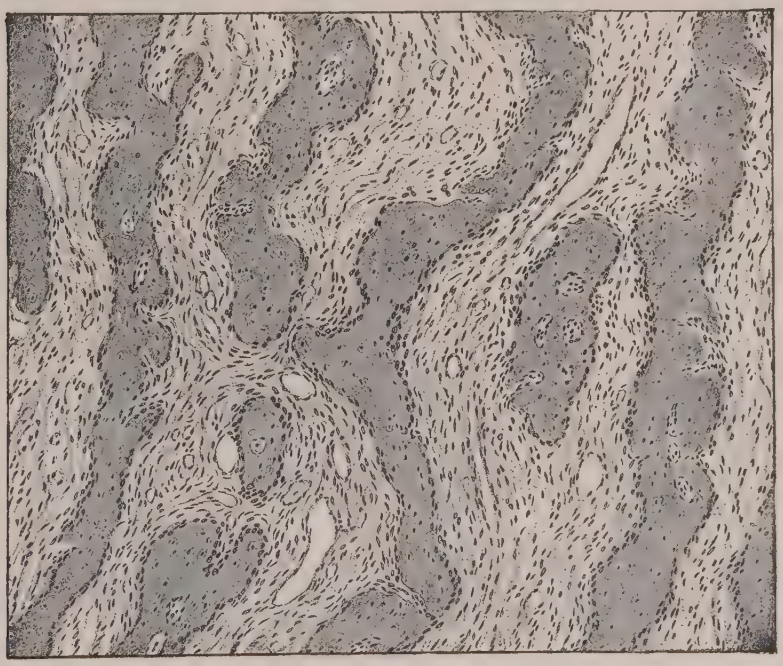


Fig. 753.—Osteoma of Lower Jaw.
Rapidly growing fibrous type.

The shape of exostoses varies greatly; they may be in the form of sharp, narrow spicula and processes, and, occurring in connection with periostitis, are called *osteophytes*. They may be polypoid in shape, or form rounded tumors with a broad base. They may form a general enlargement of the bone with much roughening of the surface; this condition is often called *hyperostosis*.

The bone beneath these new growths may be normal, or sclerosed, or rarefied, or the medullary cavity of the bone may communicate with that

of the exostosis. Exostoses are usually developed from the periosteum, sometimes in the insertion of tendons and ligaments. They are very frequently multiple, and may occur at all ages, even during uterine life.

Enostoses are developed in the interior of bones from the medulla. They may increase in size, with absorption of the surrounding bone, until they project from the surface like exostoses. Their most frequent situation is in the bones of the cranium and face.

Chondromata.—These tumors may be single or multiple, and most frequently grow from the interior of the bone, but sometimes from the periosteum. They are prone to form various combinations with other forms of tumors, as fibroma, myxoma, sarcoma, etc. They are frequently congenital, and are most common in young people. They occur most frequently in the bones of the hand and foot (Fig. 754).

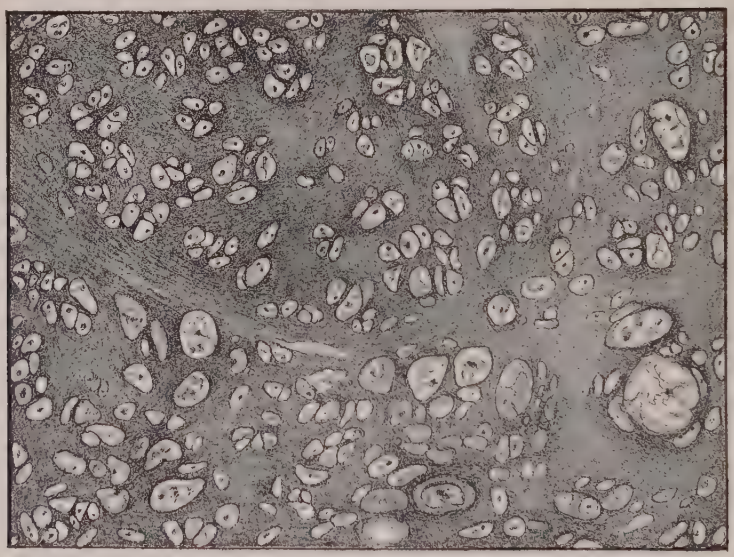


Fig. 754.—Chondroma of Humerus.

There is a form of chondroma, called *osteoid chondroma*, which develops beneath the periosteum, most frequently in the femur and tibia near the knee-joint, forming a club-shaped enlargement of the bone. The characteristic of the tissue composing these tumors is that it resembles somewhat the immature bone tissue which is seen beneath the periosteum in developing bone. It differs from cartilage in the irregular shape of its cells, in the fibrillation and density of the basement substance, and in its general vascularity. On the other hand, it has not the inorganic contents or appearance of true bone. It resembles considerably the callus tissue forming about fractures of the bones. It may, however, and most frequently does, become converted, in some parts of the tumor, into true bone. On the other hand, combinations with sarcomatous tissue are of frequent occurrence (see below).

Sarcoma is especially common in the bones. It grows from the inner layers of the periosteum or from the medulla, so that we may distinguish

a *periosteal* and a *myelogenic* sarcoma (Fig. 755). Sometimes the tumor involves the bone itself so early that it is impossible to say whether the tumor began in the periosteum or in the medulla. There is also a variety which grows close to the outside of the periosteum and becomes connected with it—*parosteal* sarcoma.

The *periosteal sarcomata* usually belong to the varieties fibro-, myxo-, chondro-, and osteo-sarcoma, more rarely to the medullary variety. They commence in the inner layers of the periosteum, pushing this membrane outward. After a time the periosteum is involved and the tumor invades the surrounding soft parts. The bone beneath may remain normal, or may be eroded and gradually disappear until the tumor is continuous with the medulla. Portions of the tumor may be calcified, or a growth of new bone may accompany its growth. The new bone usually

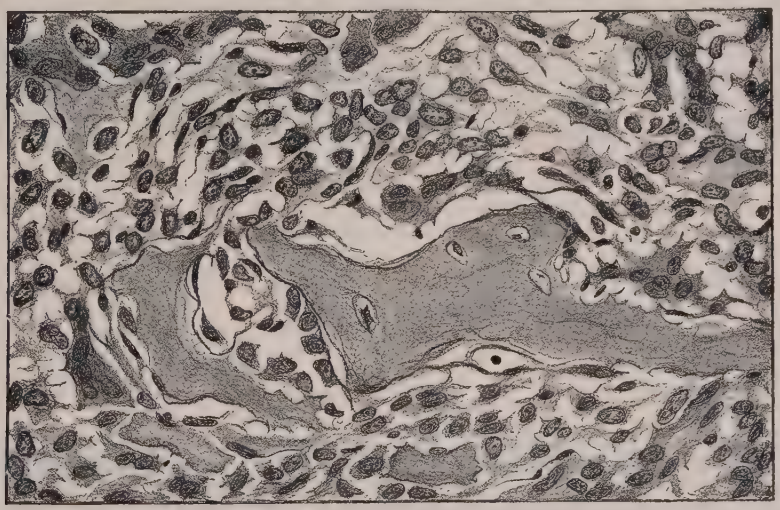


Fig. 755.—Myelogenic Sarcoma of Bone, with Giant Cells.

takes the form of plates, or spicula, radiating outward (Fig. 756). The minute structure of these tumors is very variable. The simplest—the fibrosarcomata—are composed of fusiform, round, stellate, and sometimes giant cells (myeloplaxes), in varying proportions, packed closely in a fibrous stroma. In the medullary form the stroma is diminished to a minimum and the round cells are most numerous. In the chondro- and myxo-sarcoma the basement substance may be hyaline or mucous, and the cells may follow the type of cartilage and mucous tissue more or less closely. There is a mixed form of tumor, called *osteoid sarcoma*, which is very apt to spread and to form metastases especially in the lungs. The growth consists in part of tissue corresponding to fibrosarcoma and round-cell sarcoma. In addition to this there occurs, in greater or less quantity, immature bone tissue, called osteoid tissue, which may in part become calcified, the calcification usually occurring in the central portions, leaving a softer peripheral zone. This form of tumor is most apt to occur at the ends of the long bones, and may form tumors of large size. It is often called, on account of its tendency to extend and to form

metastases, *malignant osteoma* or *osteoid cancer*. *Angiosarcomata* are of infrequent occurrence in bone.

Sarcomata may originate in the medulla—*myeloid sarcoma*—and may grow rapidly, the bone surrounding them being destroyed so that they project as rounded tumors. Most frequently new bone is formed beneath the periosteum, so that the tumor is inclosed in a thin, bony shell

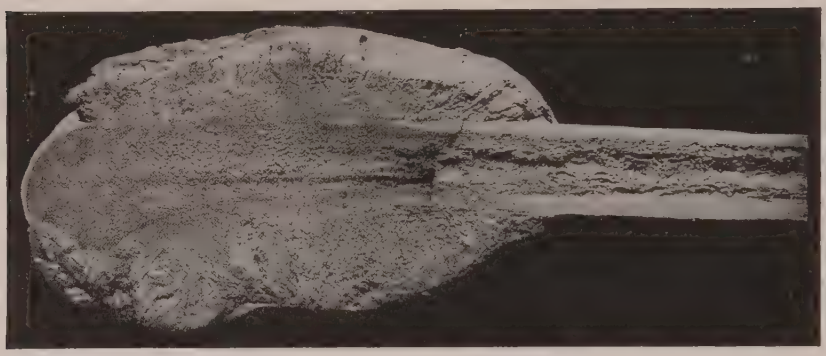


FIG. 756.—SARCOMA OF THE BONE—PERIOSTEAL.
The growth has invaded the shaft of the bone, which is fractured. Spicula of bone, new-formed in the tumor, may be seen below, passing outward from the periosteum.

(Fig. 757); sometimes there are also plates of bone in the tumor; sometimes the periosteum is unaltered; sometimes it is perforated and the tumor invades the surrounding soft parts. The tumors are frequently very soft, vascular, and hemorrhagic in parts, and are usually of the spindle-cell or round-cell variety, and not infrequently contain giant cells.

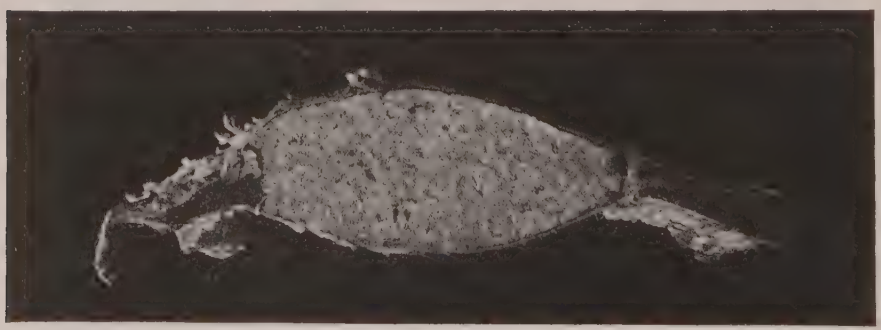


FIG. 757.—MYELOGENIC SARCOMA OF THE STERNUM.

In recent years there has been much discussion concerning the nature of these tumors. It has been found that those which are rich in giant cells are, despite their sarcomatous morphology, relatively or absolutely benign, and do not recur after thorough curettage of the cavity in which the tumor lies (page 444). There has been a great deal of discussion also as to the nature of the giant cells which occur in these tumors; some ob-

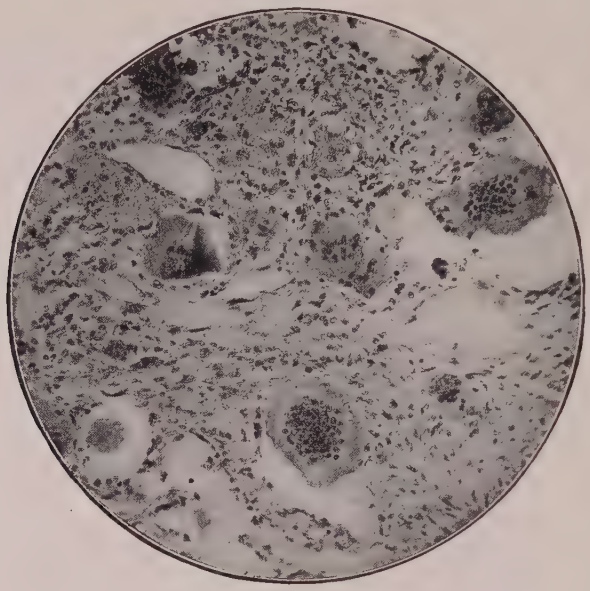


FIG. 1.—BENIGN GIANT-CELL TUMOR.

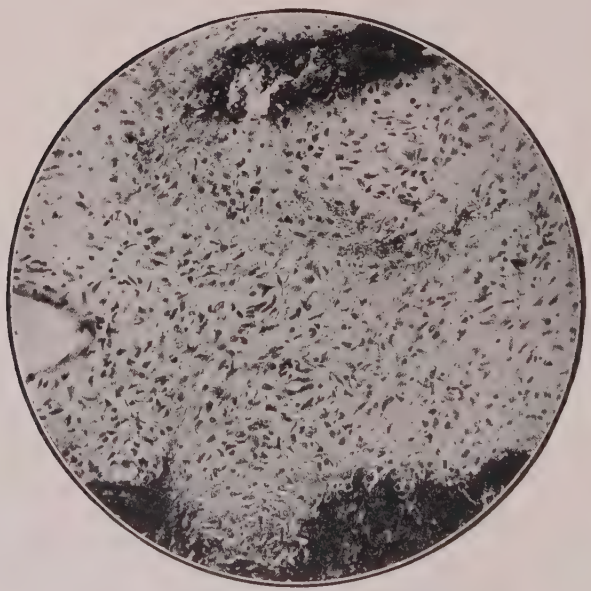


FIG. 2.—OSTEOGENIC SARCOMA

servers[1] consider them to be purely phagocytic, while others believe that they correspond to the osteoblasts of normal bone, and still others that they are true tumor cells. Instances have been reported in which the center of the tumor was softened, forming a cyst with hemorrhagic contents. There is a question whether these are truly myeloid tumors or whether they should not be classed with osteitis fibrosa in which condition giant cells are not infrequently present.

A similar type of tumor is very frequent on the tendon sheaths and the periosteum of the fingers (Fig. 239, page 444), and here, too, the clinical course shows the tumor to be of very low malignancy. Some of the tumors of this site contain cartilage also. While the question has not yet been settled, it is evident that it is not possible on the mere

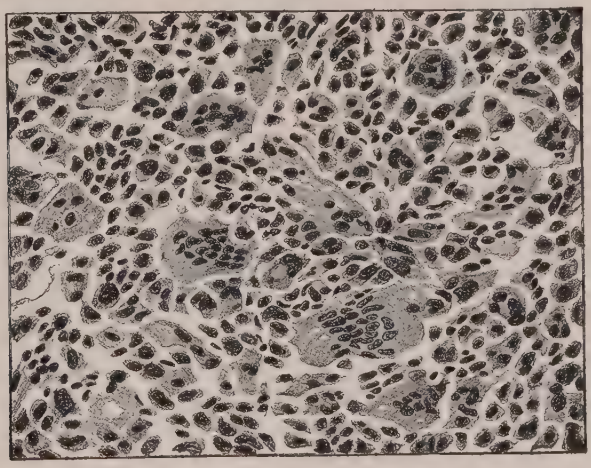


Fig. 758.—Multiple Giant-cell Tumors of Bone.
Preparation by Dr. H. S. Martland.

morphology to draw definite conclusions as to their clinical features. Some may show giant-cell morphology and yet recur locally and even extend into the neighboring tissues. One example (See Plate XIV C, Figs. 1 and 2) had the morphology of a benign tumor in some of its areas and of an osteogenic sarcoma in others. This tumor metastasized to the lungs. Such an occurrence is, however, of the greatest rarity and in general it may be stated that the giant cell tumors do not metastasize to a distance. Occasionally such giant cell tumors may be multiple in origin and an individual growth may undergo spontaneous disappearance while others are growing at the same time (Fig. 758).[2]

[1] See *Mallory, F. B.*, Principles of Pathologic Histology, Philadelphia, 1914, p. 280. Mallory thinks that many of these giant cells are due to fusion of endothelial leucocytes which have been attracted to the tumor by foreign bodies, while another type is the true tumor cell and can be distinguished by the presence of multiple mitoses which do not occur in the form due to fusion of endothelial cells. See also *Barrie, G.*, Ann. Surg., 1917, lxv, 151. *Ewing*, Arch. Surg., 1922, iv, 485.

[2] For a report of two unusual giant-cell tumors of this type, see *Martland, H. S.*, Proc. New York Path. Soc., 1915, xv, 119; *Haussling and Martland*, Ann. Surg., 1916, lxiii, 454.

Sarcomata may originate in the outer layers of the periosteum—*parosteal*. They may be as firmly connected with the bone as is the periosteal form. The periosteum may remain intact between the tumor and the bone, or it may disappear and leave them in apposition. This form is most often of the spindle-cell variety. **Endotheliomata** of bone have been described, but in most, cases if not in all, are sarcomata or hypernephromata. **Lipoma** is rare.

Angioma and Lymphangioma.—A very large number of the tumors which have been described under these names are really very vascular sarcomata. Cavernous angiomata may form between the periosteum and bone and be intimately connected with the latter. There are several cases described of cavities filled with blood in the interior of bones, which it is difficult to interpret. They have mostly been found in the head of the tibia. They are said to have consisted of single sacs composed of thickened periosteum, lined with plates of bone, and filled with fluid and clotted blood. No large vessels communicated with the sacs, but their walls were covered with a rich vascular plexus, branches of which opened into the cavity of the sac. Some of these vascular cysts are undoubtedly forms of osteitis fibrosa. Care should be taken not to confuse them with the very vascular fibromata, myxomata, and sarcomata of bone, or with aneurysm (see page 448).

Carcinoma.—Because of the lack of epithelial structures, primary carcinoma does not occur in the bones. Most of the neoplasms thus named have doubtless been sarcomata or hypernephromata. Secondary carcinoma, on the other hand, as a result of metastases or local extension, is not infrequent. Metastatic carcinoma may occur in the bones of various parts of the body at the same time, and are most apt to be secondary to carcinoma of the mamma or prostate; but metastases from the thyroid are not infrequent.[1]

The blood picture of a myelogenous leukemia is sometimes seen when the marrow is extensively invaded by metastatic carcinoma. This is probably due to stimulation of the marrow by the metabolic products of the rapidly growing masses of tumor cells.

Cysts[2] not due to parasites occur most frequently in the long bones, particularly in the femur, humerus, fibula, and tibia and are not infrequent in the metacarpals. Cysts of this type are not lined with epithelium, being produced by softening following some alteration of the bone. Originally (Virchow), they were thought to be the result of liquefaction of misplaced islands of epiphyseal cartilage, and the walls of many of these cysts do show cartilaginous elements; but this explanation has been abandoned as not valid in all cases. It is now believed that many of the bone cysts are due to a localized osteitis fibrosa[3] (page 1066), others to softening as a result of local infectious processes. Giant cells

[1] *Kanoky, J. P.*, Surg., Gynec., and Obst., 1916, xxii, 679 (bibl.).

[2] *Bloodgood, J. C.*, Jour. Am. Med. Assn., 1904, xliii, 1124; Progressive Med., 1904, vi, 181; *Skinner, M.*, Surg., Gynec., and Obst., 1915, xx, 570; *Tietze*, Ergebn. d. Chir. u. Orthop., 1911, ii, 32 (bibl.), *Lexer*, Arch. f. klin. Chir. (Langenbeck), 1906, lxxxi, 363 (good bibl.).

[3] *Bockenheimer*, Arch. f. klin. Chir. (Langenbeck), 1906, lxxxi, 236; *Haberer*, Arch. f. klin. Chir. (Langenbeck), 1910, xciii, 791.

of the same type as those seen in osteitis fibrosa may be found in the lining membrane. The contents of the cyst are usually a thin serosanguineous fluid, but it may contain myxomatous or soft fibrous material. The cysts may be multiloculated, trabeculæ being formed by bone, and in most cases are situated near or in the epiphysis. Fractures are not infrequent when the cyst is extensive, and the traumatic origin of the cysts has long been assumed; but as with tumors this is neither probable nor has it been proved.

In the bones of the jaw, especially the inferior maxilla, there arise tumors and cysts peculiar to this region, since in the process of development of the teeth from the embryonic enamel organ masses of specialized epithelium may be left deep in the substance of the jaw, to give rise later either to solid tumors or to cysts lined with epithelium. Of the solid tumors of this region there have already been discussed **adamantinoma** (page 458) and **odontoma** (page 416). Both types are usually benign, but the former may on occasion become highly malignant.

The cysts developing in the jaw[1] are, as just stated, peculiar because of their epithelial lining. Three groups of true cysts are generally recognized: (1) Those arising from the root tissues; (2) follicle cysts derived from the enamel organ and usually single; and (3) multilocular cysts arising in the jaw and growing extensively, usually distending the bone and rarefying it. The multilocular cysts may convert the entire jaw into a spongy mass, the bony walls being reduced to a few millimeters in thickness. The root cysts are usually correlated with inflammatory lesions in the teeth, but must be carefully differentiated from peridental abscess. They rarely possess an epithelial lining, for the cells, if originally present, desquamate under the inflammatory process so frequently present from infection of the cyst cavity. Occasionally, however, small areas of epithelium may persist, and in a few instances ciliated epithelium has been observed. The follicle cysts are usually lined with cylindrical epithelium, are filled with thin mucus, and may or may not contain a tooth. The multilocular cysts are usually lined with epithelium and contain a slimy, mucoid secretion, in which cholesterin crystals are sometimes found, but as the cysts are often infected, the walls may be covered with granulation tissue only. Many of the multilocular cysts are undoubtedly derived from the peridental epithelial remnants left during the development of the tooth, and hence are related to the adamantinoma; in fact, the French writers call them *epithelioma adamantinum cysticum.*

Dermoid cysts are occasionally found in connection with the bones, particularly of the skull.

Echinococcus cysts also occur,[2] and often cause spontaneous fracture.

The Joints.

For a description of the dislocations, misplacements, and injuries of the joints we refer to works on surgery.

[1] The literature of tumors and cysts of the jaw up to 1897 has been collected by *Goebel, C.*, Centralbl. f. allg. Path., 1897, viii, 128. A more recent study, with complete bibl., is by *Schmidt, M. B.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1900–01, vii, 221.

[2] *Walker, C. A.*, and *Cummins, W. T.*, Jour. Am. Med. Assn., 1917, lxviii, 839 (bibl.).

DEGENERATION.

Fatty degeneration of the cartilage cells, mucous degeneration, and fibrillation of the stroma with softening, and often roughening, of the joint surfaces, calcification, and amyloid degeneration, may occur in inflammation, or as a senile alteration, or under other conditions. The cartilage is usually, under these conditions, whiter and more opaque than normal.

INFLAMMATION. (Arthritis.)

Exudative Arthritis.—The earlier stages of acute inflammation of the synovial membranes are better known from experiments on animals than from post-mortem examinations. Among the early changes are swelling and congestion of the membrane, with increased growth and desquamation of the lining cells, and infiltration of the membrane with lymphoid cells. These conditions are soon followed by an exudation. The exact origin of much of the exudate is not clear.

In **Serous Arthritis** the accumulation of serum within the synovial sac is the most prominent lesion. The disease may terminate in recovery, or become chronic, or pass into the suppurative form. It may be incited by contusions, penetrating wounds, gonorrhea, or rheumatism, or it may occur without evident cause.

Serofibrinous Arthritis may occur under the same conditions as those which lead to simple serous inflammation. The fibrin may be present largely as flocculi in the serum, or it may form false membranes over the surfaces of the joint.

Suppurative Arthritis may follow or be associated with the above forms of inflammation. The synovial membrane is thickened and cloudy, and there may be but a moderate amount of pus in the joint, and a slight degree of infiltration of the synovial membrane with pus cells. Under these conditions resolution may occur.

In other cases the accumulation of pus in the cavity may be great, the synovial membrane and its surrounding tissue densely infiltrated with pus cells. Under these conditions granulation tissue is apt to form and the cartilages of the joints may become involved. There are swelling and proliferation or degeneration of the cartilage cells; the basement substance becomes disintegrated, ulcerates, and exposes the bone, in which osteitis, caries, rarefaction, etc., may occur. The new-formed granulation tissue may penetrate the cartilage, absorbing the basement substance, and by metaplasia the cartilage tissue may be converted into embryonal or granulation tissue. The pus may break through the capsule of the joint and form large abscesses in the adjacent soft parts. Sometimes the inflammation is not only suppurative but gangrenous, and runs a rapidly fatal course. The synovial membrane, articular cartilages, and ends of the bone all undergo a rapid suppuration and gangrene. Acute arthritis may be incited by trauma, or it may be associated with pyemia, smallpox, measles, scarlet fever, pneumonia,[1]

[1] For bibliography of pneumococcic arthritis, see *Cave, E. J.*, Lancet, 1901, i, 82.

gonorrhea, diphtheria, mumps, typhus fever, glanders, the puerperal condition, or other infectious diseases.[1] In these cases the process is apt to be suppurative, and is induced by various forms of bacteria.

Chronic Arthritis may begin as such, or it may be the result of previous acute inflammation. There is an increase of fluid in the joint. This fluid is thin and serous, or is thickened with flocculi of fibrin and epithelial and lymphoid cells, or is thick, syrupy, or even gelatinous. The synovial membrane is at first congested, its tufts are prominent. Later it becomes thickened, sclerosed, and anemic; the lining cells are destroyed, and the tufts become large and projecting. From the distention of the capsule there may be subluxations or luxations of the joint, or the capsule may be ruptured.

Rheumatic Arthritis.—An acute inflammation, usually exudative in character and involving one joint after another, is characteristic of acute articular rheumatism. The exudate is usually serous.

A chronic form of so-called rheumatic arthritis is most common in elderly persons, usually affecting several joints and advancing slowly and steadily. There is a fibrous thickening of the synovial membrane and the adjacent tissue. Fluid accumulations are not common. The articular cartilages are apt to degenerate or ossify, or become softened and fibrillated, and they may disappear. The contracting synovial membranes and fibrous tissue render the joints stiff and may cause considerable deformity. Not infrequently fibrous and bony ankyloses are formed between the ends of the bones.

Arthritis Deformans.—This name has been applied to a variety of chronic inflammation of the joints which, combined with degeneration of parts of the joint and the new formation of bone, may result in marked deformities of the part. The disease usually occurs in elderly persons and is apt to involve several joints, most frequently the hip, knee, fingers, and feet. It may be idiopathic, or due to rheumatism or to injuries, or follow an acute arthritis. The capsules of the affected joints are thickened and sclerosed. The synovial fluid is at first increased in quantity; later, diminished and thickened. The tufts of the synovial membrane become much enlarged and vascular; they may be converted into cartilage. Sometimes the capsule becomes ossified. The new bone grows from the edge of the cartilage within the capsule and its articular surface is covered with cartilage. The articular cartilages are much changed. The basement substance splits into tufts, while the cartilage cells are increased in number. Or the basement substance becomes fibrous; or it is split into lamellæ and the cartilage cells are multiplied; or there are fatty degeneration and atrophy.

As a result of these changes, larger or smaller portions of the cartilage are destroyed and the bone beneath is laid bare. The exposed bone may become compact and of an ivory smoothness. The ends of the bones are much deformed. They are flattened and made broader by irregular new growths of bone, while at the same time they atrophy. The new growth of bone starts from the articular cartilages. The cartilage cells increase

[1] For chronic streptococcus arthritis, see *Davis, D. J.*, Jour. Am. Med. Assn., 1913, lxi, 724.

in number and the basement substance grows in quantity. This growth is most excessive at the edge of the cartilage, so that a projecting rim is formed there. This projecting rim may ossify next the bone, and at the same time new cartilage may form on its surface, so that we may find large masses of bone covered with cartilage. All these changes occur in various combinations and sequences, so that joints in this condition present the greatest variety of appearances.[1]

Arthritis Uratica (Gouty Arthritis).—This lesion is characterized by the deposit of salts of uric acid in the cartilages, bones, and ligaments, and also in the cavities of joints. The deposits may be in the form of stellate masses of acicular crystals in and about the cartilage cells or in the basement substance; or they may be deposited in the fibrillar connective-tissue structures of the joint in single crystals, or in the subcutaneous tissue about the joint as white concretions. The deposits may occur in repeated attacks of the disease, and are accompanied by acute inflammatory changes. They may lead to various forms of chronic inflammation of the joints.

Tuberculous Arthritis.—This process may commence in the synovial membrane of the joint, or may extend to the joint from adjacent bone. It is characterized by the formation of tubercle tissue and granulation tissue, sometimes in great quantity, and is usually associated with secondary inflammatory and degenerative changes of surrounding parts. According to the prominence of one or other of these secondary alterations, several forms of tuberculous arthritis may be distinguished. If there is an excessive growth of granulation tissue without much suppuration, this constitutes a *fungous form.* Sometimes there is extensive *suppuration,* so that the cavity of the joint may be filled with pus, which may be discharged through openings in the skin; or there may be more or less extensive formation of abscesses, or infiltration of the soft parts about the joint with pus. In other cases there is disintegration of the new-formed tuberculous tissue and of the tissues of the joint—*ulcerative form.* The cartilage basement substance may become split into fragments and the cells degenerate, and thus deep and destructive ulcers of the cartilage may be formed. Or the new tissue may work its way through the cartilage into the bone beneath, by absorption of the basement substance of the cartilage, with or without proliferation of its cells. Caries and necrosis of the underlying bone may lead to extensive destruction. Hand-in-hand with these alterations subperiosteal new formation of bone may occur, or sclerosis of the adjacent bone tissue. There may also be a great increase of fibrous tissue about the joint. The type of lesion depends in considerable degree upon the joint involved.

This disease is most common in children and young persons. The so-called scrofulous diathesis is said to foster it, but local injuries are frequently the predisposing factors. It is most common in the large joints. It may occur in connection with tuberculous inflammation in

[1] For a valuable study of arthritis deformans, see *Nichols* and *Richardson*, Jour. Med. Research, 1909, N. S. xvi, 149.

other parts of the body, but it is frequently quite local, and may remain so for a very long time or permanently, since general infection from tuberculous arthritis is comparatively infrequent.

The process is usually slow, and may end in death. If recovery takes place before the cartilages and bones are involved, the topography of the joint is maintained; but it may be stiffened, or even immovable, from the contraction of the new fibrous tissue around it. If the cartilages and bones are diseased the joint is destroyed, and either bony or fibrous ankylosis results. Sometimes, from the change in the articulating surfaces and the contraction of the muscles and the new fibrous tissue, partial or complete dislocations are produced.

Occasionally miliary tubercles occur in the synovial membranes in cases of general miliary tuberculosis, with but little accompanying simple inflammatory change.

Syphilitic Arthritis.—Syphilitic changes in the joints are frequent in congenital luetics, and exudative arthritis has been observed, especially in the knee-joint and the spine. In adults there may be a subacute arthritis in the eruptive phase with the accumulation of serous exudate in the joint. In the tertiary stage gummata may form in the synovial membranes, setting up a perisynovitis and synovitis by exudation into the capsule, or the lesion may be primary in the bone and extend through the cartilage with final destruction of the joint.

An entirely different type of lesion is seen in neuropathic arthritis of tabes dorsalis and syringomyelia. A number of forms have been observed, one of which progresses in much the same fashion as arthritis deformans, which has led to the suggestion that these tabetic changes are simply a modified type of this form of joint disease; but the sudden appearance of the fluid, the acute swelling, the great destruction of the joint tissues, and the rapid and painless course are not characteristic of arthritis deformans. These joint changes may be very extreme and lead to the separation of considerable fragments of bone or cartilage which lie free in the joint and ultimately are smoothed off by the rubbing which occurs during motion. The destruction of the synovial membrane is frequently so extensive that spontaneous dislocation occurs, rendering locomotion impossible. In another form very extensive production of bone and cartilage may occur, greatly increasing the size of the opposed joint surfaces. Bone so formed is very spongy and may undergo spontaneous fracture.

TUMORS.

Secondary tumors of the joints as a result of local extension from the adjacent parts are not uncommon, and the tumors may be of various kinds. Primary tumors of the joints, on the contrary, are not very common. For example, some seventeen instances of sarcoma of the knee-joint are recorded, and the occurrence of tumors of this nature in other joints is of like infrequence. In most cases there is a diffuse thickening of the capsule due to tumor invasion. The tumor is usually of the myeloid variety with numerous giant cells. One instance of a xantho-

sarcoma has been recorded,[1] and a few round-cell sarcomata have been observed.

Lipoma.—A new growth of fat tissue may begin in the other portions of the synovial membrane, push this inward, and project into the joint in a mass of tufts—*lipoma arborescens.*

Fibroma occurs as a hypertrophy of the little tufts and fringes of the synovial membrane. In this way large polypoid and dendritic bodies are formed. The pedicles of these growths may atrophy and even disappear, so that the growths are left free in the cavities of the joints.

Corpora aliena Articulorum (Loose Cartilages in the Joints).—This name is given to bodies of various structure and origin, which are found free or attached by slender pedicles in the cavities of the joints. They are most frequently found in the knee; next in order of frequency in the elbow, hip, ankle, shoulder, and maxillary joints. They may be single or in hundreds. Their size varies from that of a pin's head to that of

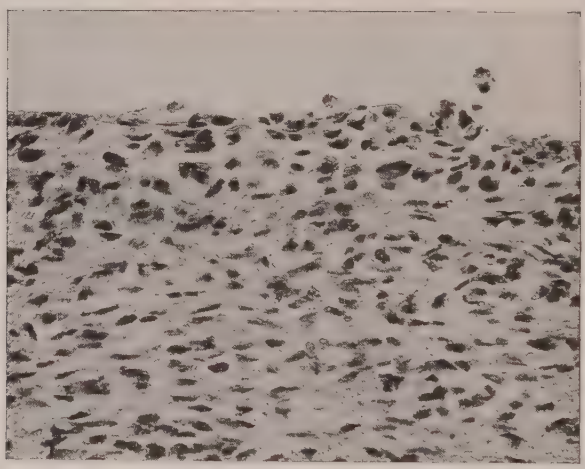


Fig. 759.—Loose Body in Knee Joint with Endothelial-like Covering. × 160.

the patella. They are polypoid, rounded, egg-shaped, or almond-shaped; their surface is smooth or faceted, or rough and mulberry-like. They are composed of fibrous tissue, cartilage, fat, or bone, either pure or mixed in various proportions (Fig. 759).

These bodies are most often formed by hyperplasia of the synovial tufts and the production in them of cartilage and bone. The usual process is that small plates of cartilage form on the inner surface of the synovial membrane, which increases in size while their outer layers ossify. These may remain fixed in the synovial membrane; or they project and become detached from it, and they then appear as flattened, concave bodies composed of bone covered with cartilage on one side.

[1] *Züllig, J.*, Cor.-Bl. f. schweiz. Aerzte, 1917, xlvii, 1368.

On the other hand, cartilage and bone may form outside the synovial membrane from the periosteum or the edges of the articular cartilages, and, pushing inward, may later become detached.

Rarely portions of the articular cartilages may be detached by violence or disease; or masses of fibrin, blood-clot, and other concretions may form in the joints in arthritis deformans, or under conditions which we do not understand.[1]

The Bursæ.

Some of the large bursæ are preformed; others originate in connective tissue, a portion of which atrophies; fluid then collects in the cavity, and

Fig. 760.—Calcification of Subacromial Bursa.
An arrow points to the remains of the bursa.

later an imperfect endothelial lining may form. The same process is responsible for the formation of the mucus-containing cysts (*ganglia*)[2] which occur so frequently about the wrist joints. After trauma, blood may collect in a bursa, distend it, and later undergo organization or complete resorption. Acute suppurative inflammation may take place if bacteria obtain entrance to the bursal cavity. Chronic inflammation, however, is a much more important and frequent lesion of the bursæ, the most characteristic example being the swelling and inflammation of the prepatellar bursæ in those who have to spend much time on their knees (*housemaid's knee* in cleaning women). The process is a connective

[1] For further details, see *Barth*, Arch. f. klin. Chir. (Langenbeck), 1898, lvi, 507; *Boerner*, Deutsch. Ztschr. f. Chir., 1903, lxx, 363; and *Schmieden*, Arch. f. klin. Chir. (Langenbeck), 1900, lxii, 542.

[2] *Thorn, J.*, Arch. f. klin. Chir. (Langenbeck), 1896, lii, 593.

tissue thickening of the wall of the bursa, distention of the lumen with exudate, and in some instances a complete organization of the contents with obliteration of the cavity itself. If any exudate remains it is thick and is often colored with blood. Small bodies of hyaline material, called *rice bodies*, may exist in considerable numbers in the inflamed bursa. Ultimately, the exudate may undergo calcification with the obliteration of the cavity. This occurs not infrequently in or about the subacromial bursa,[1] which is peculiarly subject to injury (Fig. 760).

Tuberculous inflammation may occur in a bursa, usually in connection with tuberculosis of the neighboring bone. The cavity is distended by the effusion, and tubercles with characteristic giant cells may be found in the walls.

[1] *Smith, M. K.*, Med. Record, 1917, xci, 406.

CHAPTER XIV.

THE NERVOUS SYSTEM.[1]

The Membranes and the Ventricles.

The Dura Mater Cerebralis.

The cranial dura mater consists of two layers, an outer, which forms the internal periosteum of the cranial bones and carries the meningeal arteries and veins, and an inner, which is more delicate in structure than the outer dense layer and is richly vascular. The dural sinuses are inclosed between these two layers. The inner layer of the dura is reduplicated in certain locations, forming the tentorium, the falx cerebri, the falx cerebelli, and the diaphragma sellæ. Lesions of the dura mater, therefore, are apt to be associated with lesions of the cranial bones, of the pia mater, or of the venous sinuses.

In young children the dura mater adheres closely to the inner surface of the cranial bones, in adults it is more readily detached, and in old persons it is again more adherent. Chronic inflammation of the external layers of the dura mater also renders it more adherent to the bones. The intimate relationship of the membranes with the brain and cord leads to the simultaneous affection of both by many inflammatory and other processes; but for clarity of consideration it is better to consider the lesions of the two under separate heads.

HEMORRHAGE.

Extravasated blood may lie between the dura mater and the cranial bones, in the substance of the membrane, or between the dura mater and the arachnoid.

Hemorrhages between the dura mater and the cranial bones are usually due to blows and injuries of the head, are often of considerable size, separating the membrane from the bones, and may compress the brain. They are often associated with laceration of the brain, and with hemorrhages between the dura mater and arachnoid.

Hemorrhages between the dura mater and the pia-arachnoid may take place from the vessels of either membrane. Those from the vessels of the dura may result from chronic pachymeningitis.

Hemorrhages into the substance of the dura mater are not frequent and are usually small.

Pressure on the head of the infant in delivery may cause extravasations of blood between the bones and the dura mater, as well as between the bones and the pericranium.

THROMBOSIS.

Thrombosis of the venous sinuses is not uncommon. It is often associated with inflammation of the dura mater and with injuries and inflam-

[1] The detailed anatomy of the brain can not be considered here. The student should consult Quain's Anatomy, vol. iii, part i, 11th ed., London, 1909; Lewandowsky's Handbuch d. Neurologie, Berlin, 1910–14; *Bing*, Regional Diagnosis in Affections of the Brain and Spinal Cord, 2d ed., New York, 1913; *Tilney, F.*, and *Riley, H. A.*, The Form and Functions of the Central Nervous System, New York, 1921.

mations of the brain and pia mater, of the cranial bones, of the middle ear, and of the scalp. Like thrombosis in other parts of the body, it may occur in the infectious and exhausting diseases. It may occur in apparently healthy persons without discoverable cause. The thrombi may be red or white, and firm. They may induce no secondary changes, or they may extend into the veins and induce hemorrhagic softening of the involved areas of the brain. A secondary hydrocephalus is occasionally a consequence of such thrombosis.

INFLAMMATION. (Pachymeningitis.)

This may involve the external layers of the membrane, *pachymeningitis externa*, or the internal layers, *pachymeningitis interna*. It may be either acute or chronic. The tissues of the substance of the dura mater participate to a greater or less degree in these changes, but the chief lesions are upon the surfaces.

Acute Pachymeningitis Externa is usually secondary to injuries or diseases of the cranial bones; thus it may be incited by fractures of the skull, either depressed or not, osteitis, caries, and suppurative inflammation of the internal and middle ear and of the mastoid cells. The dura

Fig. 761.—Pachymeningitis Interna Hemorrhagica—Chronic.
At the left near the vessels are connective-tissue cells containing blood-pigment.

mater is commonly congested and swollen, and may contain small ecchymoses. The inflammation is usually suppurative, and pus may accumulate between the membrane and the bone, or in the substance of the membrane. The areas of inflammation are not usually extensive. It sometimes leads to thrombosis of the venous sinuses, and sometimes gangrene of the dura mater occurs. The inflammation may extend to the inner surface of the dura mater, or to the pia mater and brain, or it may remain localized and undergo resolution.

Acute Pachymeningitis Interna may be secondary to inflammation of the external surface, or it may occur as a complication in pyemia, puerperal fever, chronic diffuse nephritis, in the exanthemata and erysipe-

las, or independently. There is a general or circumscribed production of fibrin and pus, so that the internal surface of the membrane is lined with a layer of soft, yellow exudate.

Simple Chronic Pachymeningitis consists in the formation of new connective tissue in the dura mater, by which it becomes thicker and in many cases abnormally adherent to the bones of the skull. This thickening may be general or circumscribed, and may involve the entire thickness of the membrane. Not infrequently, when the external layers are especially involved, firm adhesions to the skull occur, with ossification of the outer layers, so that shreds of the membrane containing little masses of bone (osteophytes) remain sticking to the skull when the membrane is stripped off.

Pachymeningitis Interna Hæmorrhagica.—This is an important form of chronic inflammation of the internal layer of the dura mater, characterized by the formation of layers of new delicate connective tissue with numerous very thin-walled blood-vessels from which the blood is prone to escape. The membrane may at first appear as a delicate fibrinous pellicle, with small red spots scattered through it, or it may look like a simple reddish or brown staining of the inner surface of the dura mater. Microscopical examination shows this membrane to consist of numerous blood-vessels, mostly capillaries with very thin walls, which may be distended or pouched, and which have grown out from the vessels of the dura mater (Fig. 761). Between the vessels is a homogeneous or slightly differentiated basement substance, containing a variable number of spheroidal, fusiform, or branching cells. Red blood-cells in variable quantity, blood pigment in various forms, frequently inclosed in the new cells, and small calcareous concretions (brain sand) (Fig. 762) also lie in the intervascular spaces. In more advanced stages the new membrane may become greatly thickened, its outermost layers being changed into dense fibrous tissue with obliteration of the vessels; while the more recently formed layers are similar in structure to those at first developed. Considerable blood usually escapes by diapedesis from the vessels of the new membrane in all stages of its formation. The vessels are also very liable to rupture, giving rise to extensive hemorrhages either into the substance of the membrane or between it and the pia-arachnoid. Sometimes masses of new tissue and blood, from half an inch to an inch or more in thickness, are formed in this way, greatly compressing the brain. These new membranes are most frequently formed over the convexity of the brain, but may extend over nearly the entire surface of the dura mater. Sometimes, when old, the entire membrane, densely pigmented and firm, lies loosely beneath the dura mater without compressing the brain or giving any clinical indication of its presence. The membrane may induce chronic changes in the pia mater, with or without accompanying changes in the cortical portion of the brain.

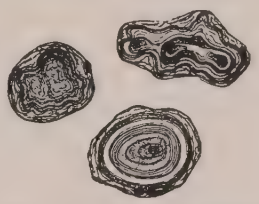


Fig. 762.—Brain Sand from Pachymeningitis Interna.

Rarely, serum accumulates between the layers of the new membranes

and in this way cysts of large size may be formed. In rare cases diffuse suppuration of the entire new membrane occurs. The slighter degrees of this form of inflammation may occasion no symptoms during life. They are not infrequently found in persons suffering from various chronic brain lesions and from chronic alcoholism, but they may occur unassociated with complicating lesions. The more advanced forms of the lesions are frequently found in idiots, epileptics, etc.

Tuberculous Pachymeningitis may occur secondarily to that form of inflammation in the pia mater or the bones, or as a part of general miliary tuberculosis. The tubercles may be situated on either surface of the membrane or in its substance, and may be single or aggregated, forming large masses.

Syphilitic Pachymeningitis manifests itself by the formation of gummata upon either the external or internal surface of the dura mater or, more frequently, by a diffuse syphilitic inflammation. These gummata may be single or multiple, and may vary greatly in size. They may be accompanied by simple inflammatory changes in the dura mater in their vicinity. They may undergo suppuration with the formation of abscess. The inflammation may extend to the pia mater, inducing simple or syphilitic meningitis and adhesions between the dura mater and pia-arachnoid. The gummata may, on the other hand, when occurring on the outer surface of the membrane, cause absorption and perforation of the bones of the skull.

TUMORS.

Fibromata and **lipomata** occur rarely in the dura mater and are of small size.

Small **chondromata** are sometimes found connected with the dura mater at the base of the brain. Small, soft, translucent growths somewhat resembling cartilage are seen under the dura. They are derived from remnants of the chorda dorsalis which remain in the clivus. Occasionally, this tissue may develop into large tumors with malignant qualities (see under Chordoma, page 413).

Osteomata.—In addition to the formation of osteophytes in chronic external pachymeningitis, plates and, more rarely, globular masses of bone may be formed in the dura mater, unconnected with the bones of the skull. They are most frequently found in the falx cerebri, but may occur elsewhere. The new bone may be dense or loose in texture, and usually produces no symptoms.

Hemangiomata and **lymphangiomata** may occur in the dura and pia.

Endotheliomata.[1]—These tumors may grow inward or outward, causing pressure on the brain or absorption and perforation of the bones; they often attain considerable size. Some of these tumors somewhat resemble certain forms of epithelioma, and have often been described as primary carcinomata. They vary in character, being sometimes formed of

[1] *Dagonet*, Arch. de méd. expér., 1892, iv, 361; *Hassin, G. B.*, Histopathology of carcinoma of the cerebral meninges, Arch. Neurol. and Psychiat., 1919, i, 705; *Lissauer, M.*, Zur Kenntnis der Meningitis carcinomatosa, Deutsch. med. Wchnschr., 1911, xxxvii, 16; *Mallory, F. B.*, The type cell of the so-called dural endothelioma, Jour. Med. Research, 1919–20, xli, 349.

densely packed masses of flattened cells with little fibrous stroma (Fig. 248, page 451), sometimes lobulated with considerable dense stroma in narrow or broad bands. In other cases, the polyhedral or cuboidal cells are conspicuously grouped around blood-vessels. Again, the cells form concentric, densely packed masses, either around vessels or around a

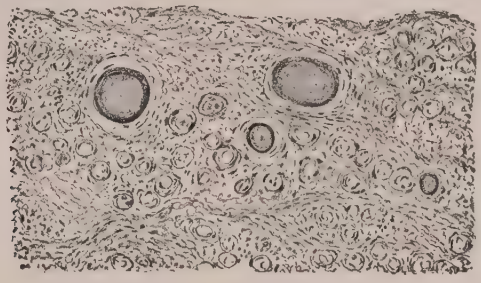


Fig. 763.—Psammoma of the Dura Mater.

central cell group (Fig. 249, page 451). These form one of the types of *psammoma*, and the concentric borders are often calcified.

Sarcomata are the most common tumors of the dura mater, and of these the spindle-cell forms are of more, the round-cell and polyhedral-cell forms of less, frequent occurrence; the melanotic types are very rare. They may grow from either surface of the membrane. Giant-cell sarcoma is derived usually from the bone and invades the dura secondarily.

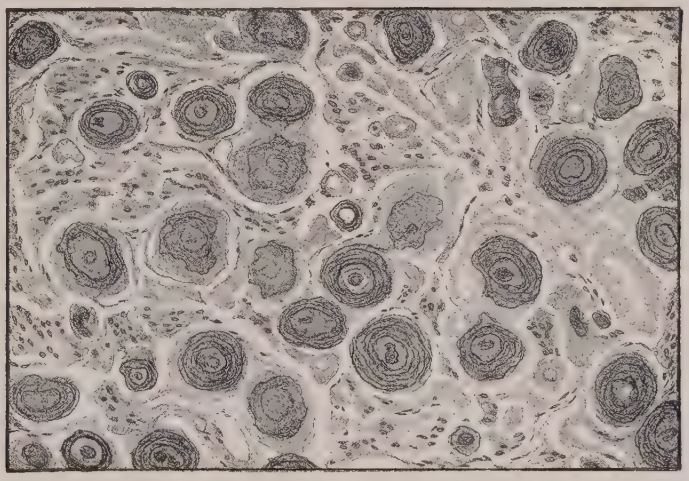


Fig. 764.—Psammoma of Brain.

Some of the round- and polyhedral-cell forms are soft and very vascular, and are apt to involve the neighboring pia mater and brain tissue, or the bones of the skull, which they may perforate. They sometimes project through the opening in the skull as fungous, bleeding masses. **Myeloma** and **chloroma** form a portion of the round-cell group.

Psammomata are small globular tumors, often multiple and pedunculated, growing from the inner surface of the dura mater. They are usually composed of tissue, fibrous, sarcomatous, or endotheliomatous in character, and contain variously shaped calcareous concretions similar in appearance to the so-called brain sand[1] (Fig. 763 and 764).

The Pia Mater Cerebralis and the Arachnoid.

General Characters of the Pia Mater and of the Arachnoid.

The external surface of the brain is invested by a connective-tissue membrane which covers the convolutions, dips down into the sulci, and extends into the ventricles. This membrane is abundantly supplied with blood-vessels, and from it numerous vessels extend into the brain, so that any disturbance in the circulation of the blood in the pia mater involves a disturbance in the circulation of the blood in the brain also.

The connective tissue which makes up the pia mater is arranged in a series of membranes and fibers reinforced by elastic tissue, forming a spongy membrane containing numerous cavities more or less filled with fluid. These cavities are continuous with the perivascular spaces which surround the vessels that pass from the pia mater into the brain. The outer layers of the pia mater are the most compact, and are covered on their outside surface by a continuous layer of endothelial cells. This external layer, the arachnoid, is a serous membranous sac, consisting of an outer layer, in contact with the dura, and an inner layer, in contact with the pia, which completely incloses the brain and spinal cord, but does not dip into the sulci and fissures of the brain. The space between the arachnoid and the pia is the subarachnoid space, and contains the cerebrospinal fluid. At some points the arachnoid is widely separated from the pia, thereby forming wide spaces filled with fluid, which are known as the cisterns. The deeper layers of the pia contain the blood-vessels. The membranes and fibers which compose the pia mater are partly coated with cells which have irregular and delicate cell bodies and large, distinct nuclei.

Along the borders of the longitudinal fissure, and, more rarely, on the under surface of the brain, are a number of small, white, firm, irregular bodies, the *Pacchionian bodies* or *granulations*, which are reduplications and thickenings of the arachnoid. They vary in size, in number, and in the extent of the surface of the hemispheres which they cover, increase with age, and are more numerous in males than in females. They serve as filters for the cerebrospinal fluid, which makes its escape into the general circulation through them. They may perforate the dura mater, or, more rarely, the wall of the longitudinal sinus, and may produce erosions of the skull bones. They are composed of fibrous tissue and may undergo fatty or calcareous degeneration.

The pia mater is frequently thickened, opaque, and white, either in diffuse patches or, more commonly, along the course of the vessels. In other cases single or multiple small white spots, of the size of a pin's head or smaller, may be seen in the membrane, not appreciably elevated above the surface, but due to localized thickening. These slight opacities of the pia mater are commonly believed to be dependent upon repeated congestions of the membrane or upon chronic meningitis, but there is no evidence that this is always the case. They are most frequently found in old persons, but may exist at any age, and do not necessarily indicate the pre-existence of disease.

The amount of blood contained in the vessels of the pia mater after death varies greatly, and is by no means a reliable indication of the amount present during life. In edema of the brain and pia mater the vessels of the latter may contain but a small amount of blood.

EDEMA.

The quantity of serum beneath the pia mater and infiltrating its tissue is very variable in amount. It may accumulate as a result of atrophy of the brain substance or of venous hyperemia, and sometimes is, and sometimes is not, accompanied by edema of the brain substance.

[1] For a study of psammoma, consult *Ernst, P.*, Zieglers Beitr., 1892, xi, 234.

It may be diffuse or localized. It is not infrequent to find in hospital patients suffering from chronic nephritis, cardiac or pulmonary disease, or chronic alcoholism, a very considerable amount of serum in this situation, though the patient has been free from cerebral symptoms. In other cases a serous effusion may accompany grave cerebral symptoms. It is necessary to be very careful in judging of the importance of this accumulation of fluid, especially in determining the cause of death in the absence of other marked lesions.

It should always be borne in mind that an accumulation of fluid beneath the pia mater and in its meshes may occur as a result of post-mortem changes.[1]

HYPEREMIA AND HEMORRHAGE.

Hyperemia.—The pia mater may be hyperemic in early stages of meningitis, in delirium tremens, in epileptic convulsions, in infectious diseases, and in poisoning. The hyperemia may be due to the pressure of exudates or tumors on the veins, or to general or local lesions of the circulatory system. The time which elapsed between death and the autopsy, the position in which the body has lain, and the coagulability of the blood, may have an important bearing upon the amount and situation of blood in the pia.

Hemorrhage.—This may occur either into the space between the dura and the arachnoid or between the arachnoid and the pia —*intermeningeal hemorrhage*—or in the meshes of the pia or between the latter and the brain. It may be due to injury, to rupture of aneurysms or otherwise diseased blood-vessels, to thromboses of the venous sinuses, or to conditions which we are unable to ascertain. Hemorrhages without known cause not infrequently occur in the substance of the pia mater in young children, but in adults they are apt to be the result of injury. Multiple ecchymoses, however, in the substance of the pia mater sometimes occur in infectious diseases and also in acute inflammation of the pia mater. Hemorrhages in the brain substance may lead to the accumulation of blood beneath or in the meshes of the pia mater. Intermeningeal hemorrhage in infants as a result of injury during birth is not uncommon. Small, or sometimes considerable, extravasations of blood may occur from diapedesis, and sometimes, as a result of chronic congestion, degenerated blood-pigment collects along the walls of the vessels. The extravasated blood in meningeal hemorrhage, if small in quantity, may be largely absorbed, leaving a greater or smaller accumulation of pigment at the seat of the hemorrhage. Such pigmentations may last for a long time.

INFLAMMATION. (Meningitis; Leptomeningitis.)

We distinguish acute, chronic, tuberculous, and syphilitic meningitis.

Acute Meningitis may occur as the characteristic lesion of epidemic cerebrospinal meningitis; it is a not very infrequent complication of pneumonia, influenza, typhus and typhoid fever, the exanthemata, and

[1] For study of edema of the pia arachnoid, see *Stillman, C. K.*, Arch. Int. Med., 1911, viii, 193.

chronic diffuse nephritis; it may be secondary to injuries and inflammation of the cranial bones, of the dura mater, and of the middle ear, and it sometimes occurs as an independent infectious process.

In acute meningitis the inflammatory process is apt to extend downward and involve the pia mater of the cord. It may also involve the ependyma of the ventricles, and cause the distention of these cavities with serum. This latter condition is especially frequent in young children.

It is convenient to consider two varieties of acute meningitis, one in which there is cell proliferation with little or no exudate, the other in which exudate is present. In many cases at least, the first may be the early stage of the latter form.

1. Acute Cellular Meningitis.—The pia mater is congested, its surface is dry and lustreless, and it is somewhat opaque. The changes in the gross appearance of the membrane are not marked and are easily overlooked, but the minute changes are more decided. There is a pro-

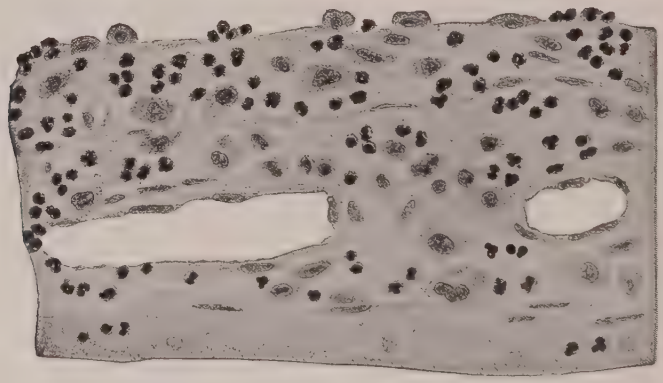


Fig. 765.—Acute Exudative Meningitis.
Showing distention of the meshes of the pia mater of the brain with fluid, in which are leucocytes and exfoliated endothelium, the latter undergoing proliferation.

liferation of the endothelial and connective-tissue cells of the pia, and often a moderate collection of fluid and leucocytes in the meshes of the pia. This cell proliferation may involve the pia mater over most of the surface of the brain. This form of meningitis is of frequent occurrence and is attended with the ordinary clinical symptoms of acute meningitis.

2. Acute Exudative Meningitis is characterized by the accumulation, chiefly in the meshes of the pia mater and along the walls of the blood-vessels, of variable quantities of serum, fibrin, and pus. Sometimes one, sometimes another of these preponderates, giving rise to serous, fibrinous, or purulent forms of the inflammation. The absolute quantities of the exudation also vary greatly. In some cases death may occur with so slight a formation of exudate that to the naked eye the pia mater may look quite normal or perhaps only moderately hyperemic or edematous; the microscope, however, will reveal in these cases pus cells in small numbers, newly formed connective-tissue cells (Fig. 765

and Fig. 766), and sometimes flakes of fibrin in the meshes of the pia and along the walls of the vessels. In other cases turbid serum in the meshes of the membrane is all that can be seen and the microscope shows the turbidity to be due to pus cells or to a small amount of fibrin. Again, either with or without marked edema of the pia mater, yellowish stripes are seen along the sides of the veins, sometimes appearing like faint

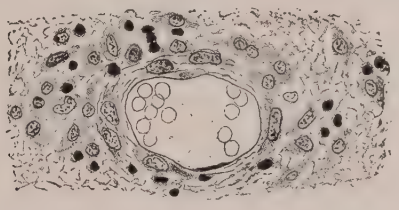


Fig. 766.—Acute Exudative Meningitis.
Proliferation of connective-tissue cells and extravasation of leucocytes in the adventitia of a small blood-vessel of the pia mater.

turbid streaks, at other times dense, opaque, thick, and wide, and almost concealing the vessels. These are due to the accumulation of pus cells and fibrin in large quantities along the vessels, and are best seen and most abundant around the larger veins which pass over the sulci. In still other cases the infiltration with pus and fibrin is so dense, thick, and general, that the brain tissues, convolutions, and most of the vessels

Fig. 767.—Acute Exudative Meningitis.
a, Convolutions of cerebrum; *b*, pia mater thickly infiltrated with pus; *c*, blood-vessels entering brain from pia and surrounded by a zone of pus cells; *d*, congested blood-vessels of pia mater; *e*, smaller blood-vessels of pia, around which pus cells are collected in dense masses.

of the pia mater themselves are concealed by it. This pus is usually of a greenish yellow color, and is sometimes so thick as to form a sort of cast of the brain surface at the seat of the lesion (Fig. 767). Sometimes extravasated red blood-cells are mingled with the other exudations, as the result of diapedesis. Microscopical examination shows numerous white blood-cells sticking to the walls of the veins and capillaries, or

blocking the vessels. It is evident that a large part of the pus cells accumulate as the result of emigration. The connective-tissue cells of the pia mater may be detached from their places or degenerated. The endothelial cells and other connective-tissue cells may proliferate. In some cases there are considerable accumulations of pus between the pia mater and the brain substance and along the vessels which enter the latter. More rarely pus is found upon the free surface of the membrane. The brain substance may be compressed by the accumulated exudate, so that the convolutions are flattened. The cortical portion of the brain may be simply infiltrated with serum—edematous—or it may undergo degenerative changes, or it may be the seat of punctate hemorrhages. Not infrequently the inflammation extends to the ventricles, which may contain purulent serum, and to the pia mater of the cord. This form of inflammation is most frequent on the convexity of the brain, but may

Fig. 768.—Fatty Degeneration of Cells Along the Blood-vessels of the Pia Mater after Exudative Meningitis.

From the pia mater of a child five years old.

extend or even be confined to the base. It may be localized, but frequently extends widely over the surfaces of the hemispheres.

When recovery from acute exudative meningitis occurs there may be fatty degeneration of the cells which have accumulated in the pia mater, particularly along the vessels (Fig. 768), and this may produce white patches in the membrane and threads along the blood-vessels, which resemble the appearance of an accumulation of exudate in the acute stage. Fatty degeneration of the blood-vessels and cells of the pia mater may also occur without acute inflammatory changes.

Sometimes, in children and young adults, inflammatory changes in the ventricles persist for days and weeks after the subsidence of the inflammation of the pia mater.

For a discussion of the bacterial excitants of exudative meningitis see page 260.[1]

[1] The close topographic relationships which the nasal cavities and the middle ear bear to the meninges are significant in this connection on account of the possibility of the transmission to the brain membranes of bacteria not uncommonly present and usually harmless in the former situations.

Chronic Meningitis.—The entire pia mater may be involved or the inflammation may be confined to the base alone (basilar meningitis), or to the convexity alone, or to circumscribed patches of the membrane. The pia mater is thickened and opaque, the thickening being sometimes very considerable. There is a formation of new connective tissue and this may be associated with accumulation of pus, fibrin, and serum; the relative quantity of these inflammatory products varies in different cases. Firm and sometimes extensive adhesions may be formed between the dura mater and the pia mater. Not infrequently the cortical portions of the brain participate in the process, and there is an infiltration of small spheroidal cells around the blood-vessels, thickening of the walls of the vessels, and degenerative changes and atrophy of the nerve tissue. New connective tissue may also form in the brain substance, which may become closely adherent to the pia mater. The ventricles of the brain also may contain an increased amount of serum and may be dilated, the ependyma may be thickened and roughened. This form of inflam-

Fig. 769.—Miliary Tubercle of the Pia Mater of a Child.
There is an area of caseation at the center; on the right of this are two giant cells; there is a peripheral zone of small cells. The leucocytes are increased in the meshes of the pia.

mation may be the result of injury or disease of the cranial bones, or secondary to chronic pachymeningitis or to inflammation of the brain substance. It may occur in the vicinity of tumors of the brain or meninges. It may be a complication of chronic diffuse nephritis and cerebral arteriosclerosis or the result of chronic alcoholic poisoning. It may occur in marked form in general paresis of the insane.

Tuberculous Meningitis.[1]—This is especially characterized by the formation in the pia mater of miliary tubercles, associated with more or less well-marked exudative inflammation. It may occur in adults or in children, but is more common in the latter. The dura mater may be unchanged, or its inner surface may be sprinkled with miliary tubercles. The pia mater may or may not be congested; it may look dry on the surface or it may be edematous. Usually the brain seems to fill the cerebral cavity to an unusual degree, and the convolutions are flattened. If the pia mater be edematous the serum may be clear, or turbid with pus and fibrin. The membrane may present any of the general appearances of exudative meningitis, but always in addition to these, and sometimes without them, are found miliary tubercles. These may be few and widely scattered, or present in great numbers. They are most numerous along the blood-vessels, but may occur anywhere. They are usually abundant

[1] For a thorough study of the clinical symptoms and pathology of tuberculous meningitis, see *Meyers, A. E.*, Am. Jour. Dis Child., 1915, ix, 427.

at the base of the brain. On the convexity they are most common along the surfaces of the sulci. Some of the tubercles are so small as to be scarcely visible or entirely invisible to the naked eye; others are as large as a pin's head or larger. They may be formed in the membranous prolongations of the pia mater which dip into the sulci, around the vessels which enter the brain substance, in the choroid plexus and ependyma of the ventricles, and may exist in the spinal cord. The miliary tubercles have the usual structural characters of focal tuberculosis in connective tissue (Fig. 769).

In children the ventricles are usually more or less distended by an accumulation of transparent or turbid serum, and the walls of the ventricles may be studded with miliary tubercles (see Fig. 770). In adults the ventricles are less frequently involved. The brain tissue around the ventricles is often softened. The central canal of the spinal cord may also be dilated. It is the dilatation of the ventricles which causes the flattening of the convolutions, and the flattening is usually in direct proportion to the amount of accumulated fluid.

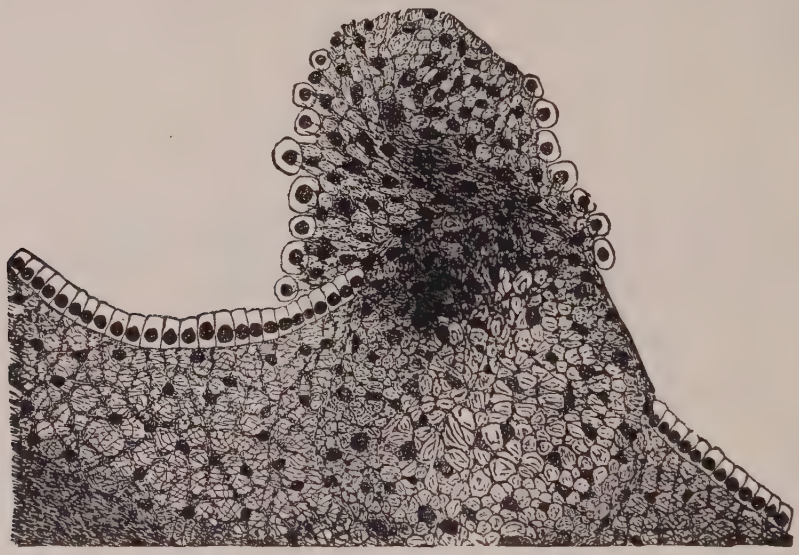


Fig. 770.—A Miliary Tubercle of the Ependyma of the Lateral Ventricle. This shows an early stage of tubercle formation on the ependyma without marked caseation.

Owing to the frequency of the dilatation of the ventricles with serum in children, the disease is often called *acute hydrocephalus*. In both children and adults the tuberculous inflammation may produce large masses of tuberculous tissue, which undergo cheesy degeneration, and may involve the brain tissue. In almost all cases of tuberculous meningitis there is tuberculous inflammation in other parts of the body.

Miliary tubercles in the choroid of the eye are present in a considerable proportion of cases. The cortex of the brain may be hyperemic, and punctate hemorrhages may be present in the cortex and in the pia mater.

Syphilitic Meningitis.—In this form of inflammation, which is usually circumscribed, there is a development of gummata of various sizes, frequently associated with simple inflammation of the membrane, either with the formation of serum, fibrin, and pus, or with the development of new connective tissue and consequent thickening of the membrane. The gummata may form in the pia mater covering the convexity, or at the base of the brain. They may grow outward, involving the dura mater; or inward, encroaching upon or involving the brain tissue. Although usually circumscribed, syphilitic inflammation may occur as a diffuse thickening of the membrane, usually over the base of the brain and along the blood-vessels and involving the sheaths of the cranial nerves. The ependymal lining of the ventricles often presents a granular appearance due to reduplications of the ependymal cells. The syphilitic nodules, including the gummata and new-formed connective tissue, are often very small, but may be as large as a hen's egg. (See, for further details, page 1200.)

TUMORS.

Hematoma.—In chronic pachymeningitis of long standing the new connective tissue may form large, flat cysts between the dura mater and the pia mater, which may compress the surface of the brain. The blood originally contained in these cysts may be absorbed and replaced by serum, the attachments to the dura mater may disappear, and the whole appearance becomes that of an independent cyst between the dura mater and the pia mater. **Fibroma, lipoma, myxoma, chondroma, osteoma,** and **cholesteatoma** (page 1204) are of rare occurrence.

Endotheliomata.—These tumors are of not infrequent occurrence, and may grow from the pia of the cerebrum or cerebellum or from the choroid plexus. They may be single or multiple.

Some of them are composed of a connective-tissue stroma which incloses regular spaces filled with large, flat, nucleated cells. These may resemble carcinoma. Some of them are composed of a connective-tissue stroma which forms cavities lined with cylindrical epithelium. In such tumors the stroma may grow so as to form papillæ covered with cylindrical epithelium; or in addition there may be mucous degeneration of the stroma. In some of them there is a connective-tissue stroma which contains large numbers of blood-vessels. Around these blood-vessels are arranged regular masses of polyhedral cells (Fig. 771 and 772).

In some endotheliomata the stroma is scanty. The cells are numerous, large, flat, and arranged in little globular masses or nests (Fig. 248, page 451). If in these little nests there is a deposition of the salts of lime, forming concretions like the so-called "brain sand," the tumor is called a *psammoma*. Some of the tumors seem to be formed of very thin, nucleated membranes arranged concentrically like the layers of an onion.[1]

Sarcoma.—Tumors belonging to the ordinary types of round-cell and fusiform-cell sarcoma and of myxosarcoma are occasionally found.

[1] For a critical review of these and other pial tumors, with bibliography, see *Bostroem, E.*, Centralbl. f. allg. Path., 1897, viii, 1.

FIG. 771.—ENDOTHELIOMA OF THE CEREBELLUM ORIGINATING IN THE PIA MATER. Showing general appearance of the tumor (see Fig. 772).

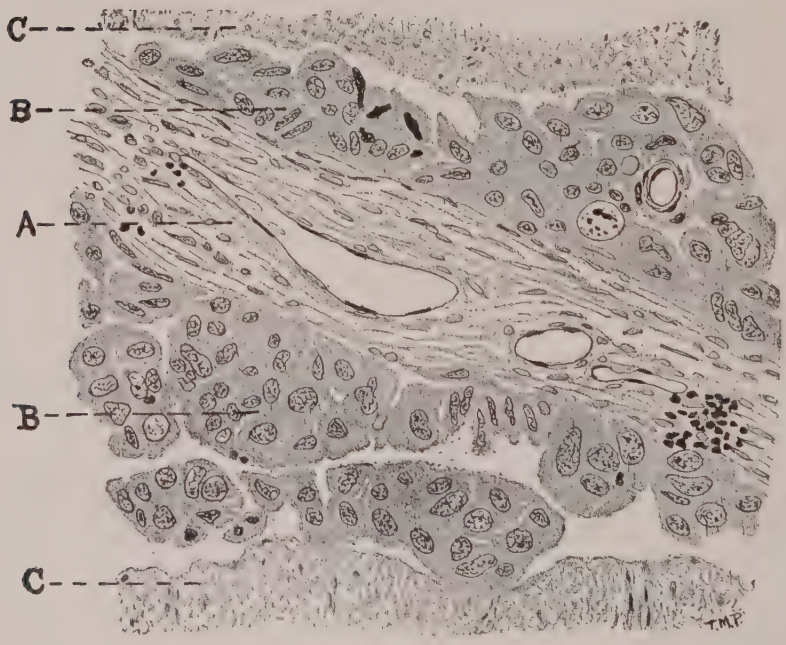


FIG 772.—ENDOTHELIOMA OF THE PIA MATER OF THE CEREBELLUM.

From specimen shown in Fig. 771, more highly magnified. A, Section of pia mater dipping into a sulcus; B, tumor cells growing at each side of the pia; C, surface of cerebellar convolutions.

Cysts.—Small cysts are often found in the choroid plexus. Rarely such cysts may reach a larger size, even as large as a pigeon's egg. Cysts of the pia mater containing serum, with walls and septa of connective tissue, and compressing the brain have been described.

Variously shaped **pigment cells** not infrequently occur in the pia mater, either scattered or sometimes in considerable masses; they seem to have little pathological significance, except as forming the starting point of the very infrequent melanotic tumors which occur in this region. Not infrequently thin plates of newly formed **bone** are found in the pia mater, associated with a thickening of the membrane.

PARASITES.

Cysticercus has been observed in the pia mater.

The Dura Mater Spinalis.

The dura mater spinalis, unlike that of the brain, does not serve as periosteum to the bones forming the cavity, so that the lesions of the two membranes differ somewhat.

HEMORRHAGE.

Hemorrhage may occur, as the result of injury, between the dura mater and periosteum, or it may occur in tetanus, as a result of circulatory changes induced by muscular spasm, or in the asphyxia of newborn children. Small hemorrhages on the surfaces of the membrane may occur as the result of inflammation. Serous fluid may accumulate outside of the dura mater as a result of post-mortem changes, or in connection with circulatory or inflammatory changes in the membranes.

INFLAMMATION. (Pachymeningitis.)

Acute external pachymeningitis is usually secondary to disease or injury of the spinal column, and may result in collections of pus between the dura mater and periosteum, usually most abundant posteriorly. **Hemorrhagic pachymeningitis** occurs in the dura mater spinalis, with the formation of products similar to those observed in the brain, in the chronic insane, and in drunkards. **Simple chronic pachymeningitis interna,** with the formation of new connective tissue containing brain sand, is not infrequent. The new tissue may form minute projections from the surface, or, when more abundant, may take the form of **psammomata. Tuberculous inflammation** of the dura mater spinalis may occur in connection with tuberculous meningitis, or be secondary to tuberculous inflammation of the vertebræ.

TUMORS.

Fibromata, lipomata, chondromata, myxomata, endotheliomata,[1] and **alveolar sarcomata** occur in the dura mater spinalis as primary tumors.

[1] *Howe, H. S.*, Extensive spinal arachnoid fibroblastoma, Neurol. Bull., 1921, iii, 216.

Carcinomata and **sarcomata** may be found as secondary tumors. Small plates of newly formed **bone** are of rare occurrence.

PARASITES.

Echinococcus developing outside of the spinal canal may perforate the dura mater; or the cysts may lie between the dura mater and the pia mater.

The Pia Mater Spinalis and the Arachnoid.

It is difficult in most cases in the pia mater, as well as in the dura mater spinalis and in the spinal cord, to judge with certainty, from the appearances after death, of the blood contents of the vessels of these parts during life. The same is true of abnormal quantities of serum found after death. The veins of the pia mater, especially in the posterior region, may be greatly distended with blood after death, without pre-existing disease; and the intermeningeal space may contain much fluid under the same condition.

Between the pia and the dura is a definite membrane, the arachnoid. It contains no blood-vessels, and receives its nutrition from the spinal fluid which circulates in the space between the arachnoid and the pia, the so-called subarachnoid space.

HEMORRHAGE.

Hemorrhages may occur from injury, in connection with severe convulsions, or in general diseases such as the hemorrhagic diathesis, scurvy smallpox, etc. The hemorrhages under these conditions, except from injury, are not usually extensive. But in some cases of injury or cerebral apoplexy, from the bursting of aneurysms of the basilar or vertebral arteries, and in other cases in which we cannot find a cause, a very large quantity of blood may collect between the dura and pia mater.

INFLAMMATION. (Meningitis.)

Acute exudative spinal meningitis occurs under essentially the same conditions and with essentially the same post-mortem appearances as acute cerebral meningitis, though it is less frequent. The exudate is apt to be most abundant in the posterior portions. It may be associated with a similar inflammation of the pia mater cerebralis, and the inner surface of the dura mater may be involved. The disease may be circumscribed, but usually affects the entire length of the membrane.

Chronic spinal meningitis is not infrequent, manifesting itself in the formation of larger or smaller patches of new connective tissue or in thickenings of the pia mater. The pia-arachnoid and dura mater may thus be firmly united in places by adhesions, or the pia mater may become closely adherent to the substance of the cord.

Not very infrequently large numbers of pigment cells are found in the pia mater spinalis, sometimes giving it a distinct gray or blackish color. This change is not due to a previous malarial infection.

Tuberculous inflammation is usually associated with a similar condition of the pia mater cerebralis, in which case the lesion is most marked in the upper portions of the cord; but it may extend over the entire mem-

brane. The conditions under which it occurs and the character of the lesions are similar in both.

TUMORS.

Fibromata, myxomata, sarcomata, and **endotheliomata** have been found.

Small plates of **cartilage** and **bone** (Fig. 773) are sometimes found in the pia mater.

PARASITES.

Cysticercus sometimes occurs in the meshes of the pia mater.

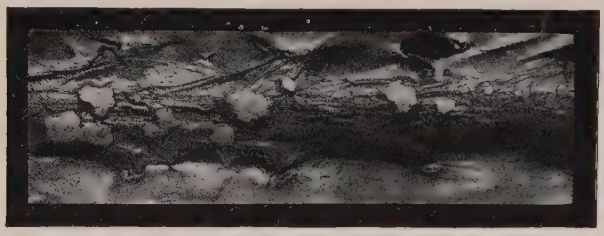


FIG. 773.—PLATES OF BONE IN THE PIA MATER SPINALIS.

THE VENTRICLES OF THE BRAIN. THE EPENDYMA AND CHOROID PLEXUS.

GENERAL CONSIDERATIONS.

As the lymph-spaces of the pia mater and the ventricles of the brain are in communication, it might be supposed that they would share alike in the accumulation of fluids. This, however, is not the case. The membranes of the brain may be highly edematous while the ventricles contain about the normal quantity of fluid; or, on the other hand, the ventricles may be widely dilated and the pia mater unusually dry. Many of these varying conditions may be understood by remembering that the skull and spinal canal form a closed cavity, and that accumulations of fluid in one part must be at the expense of some material occupying other parts, either blood, serum, or brain tissue. It is not always easy to see, however, exactly how the compensation occurs.

There may be an unusual amount of fluid in the ventricles of the brain as a result of post-mortem change; in connection with senile or other atrophy of the brain, or in the general vascular changes which lead to edema of the brain; in connection with inflammation of the meninges or of the ependyma; or under conditions which we do not understand, as in some cases of congenital and acquired hydrocephalus. Accumulations of fluid in the ventricles are often called *internal hydrocephalus* to distinguish them from accumulations in the meninges—*external hydrocephalus.*

INFLAMMATION. (Ependymitis.)

Acute Ependymitis.—In this condition, which may occur by itself, but is usually associated with inflammation of other parts of the brain, the ependyma is congested, the vessels are more prominent than usual and are often tortuous. The ependyma and the adjacent brain tissue may be thickened and infiltrated with pus cells, and the surface of the ependyma covered with fibrin and pus in variable quantity (Fig. 774). The cavities of the ventricles may contain purulent serum. Small hemorrhages may also be present in the tissue of the ependyma. This, as well as other forms of inflammation, is more common in the lateral ventricles than in the others, but not infrequently involves the fourth ventricle. The choroid plexus may participate in the inflammatory changes of the ependyma. Tuberculous inflammation of the ependyma is, as above mentioned, a not infrequent accompaniment of tuberculous meningitis.

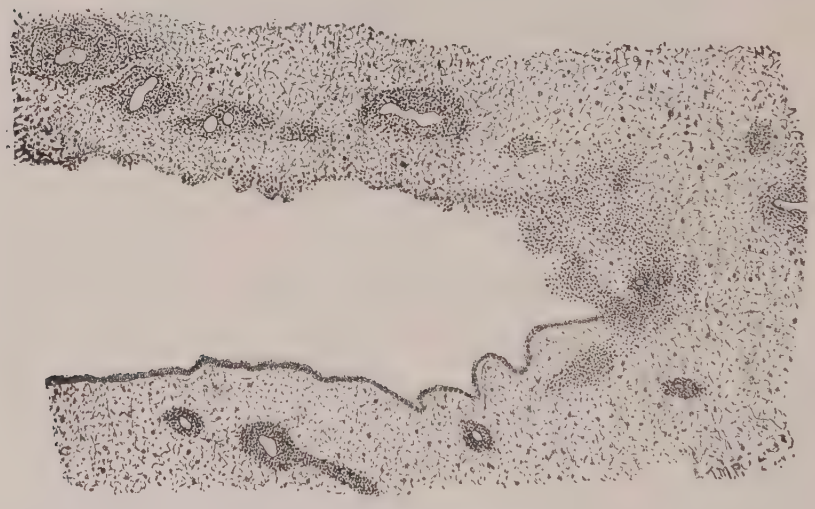


Fig. 774.—Acute Ependymitis.
Showing replacement of the epithelium of the ventricle by inflammatory exudate: collections of pus cells near the epithelium and about the adjacent small blood-vessels.

Chronic Ependymitis.—This lesion, which is much more common than simple acute inflammation of the ependyma, occurs under a variety of conditions, being most frequently seen in paresis, cerebral arteriosclerosis, and chronic encephalitic states. The ependyma is thicker, whiter, and more opaque than normal, so that the vessels may be nearly or quite invisible. The thickenings may occur in patches or diffusely, and the surface of the ependyma may be smooth, or roughened and granular. On microscopical examination the surface of the ependyma may be covered with the usual epithelium, but the new neuroglia tissue which forms beneath it often raises it up in places, causing the roughness of the surface. The new tissue is usually rather loose in texture and

may contain many small spheroidal cells; but it may be dense in texture and contain few cells. The brain tissue beneath the thickened ependyma may be softened or infiltrated with cells. The sides of the ventricles may be grown together in places by the adhesion of the thickened and roughened ependyma. The ventricles usually contain more serum than normal, and sometimes this accumulation is so great as to cause an enormous dilatation of them. The accumulation of fluid and the dilatation of the ventricles being the most marked feature in all this class of lesions, they are often called *chronic hydrocephalus*, but in many cases we have no evidence that the change in the ependyma is an important or even primary factor.

Hydrocephalus.[1]—We may, for convenience of study, consider three classes of cases of hydrocephalus: first, *congenital hydrocephalus in young children;* second, *secondary hydrocephalus in children and adults;* third, *primary hydrocephalus in adults.*

For an understanding of the conditions which lead to hydrocephalus, it is important to recall some of the facts concerning the production and distribution of the cerebrospinal fluid.[2] The fluid is presumably a true secretion from the ependymal cells of the choroid plexuses. Additional fluid may be supplied by the cerebral lymphatics, which empty into the spaces of the arachnoid. The major quantity is set free in the lateral ventricles, passing by the foramen of Monro to the mesial ventricles, from which it escapes by the foramina of Luschka and Magendie into the subarachnoid spaces. From here the excess of fluid enters the dural sinuses, probably through the intermediary of the arachnoid villi, and also from the subarachnoid space through the process of osmosis. We may, therefore, again classify hydrocephalus into, first, *obstructive hydrocephalus*, due to obstruction at any part of the path which the fluid traverses, and, second, *non-obstructive hydrocephalus*, due to increased secretion or diminished absorption of the fluid. It will thus be obvious that inflammatory or mechanical obstruction along any portion of the tortuous course followed by the cerebrospinal fluid may set up stasis; and it is not difficult to see that even thrombosis of the sinuses may accomplish the same interference with the necessary removal of the continuously secreted fluid, whose amount, it has been estimated, is not less than 500 c.c. per twenty-four hours.

1. Congenital Hydrocephalus.—The lesion may be in an advanced stage at the time of birth, or it may be scarcely evident or but moderately developed. It may progress rapidly and cause the early death of the child, or it may develop gradually or come to a standstill. In the more marked forms of the disease the ventricles are widely dilated (Fig. 759) and filled with serum, which is usually transparent. Not only the lateral ventricles, but also the third and fifth, may be involved; the fourth is less apt to participate in the lesion, although it is sometimes dilated, as well as the central canal of the cord.

[1] Consult *Margulis*, Arch. f. Psychiat., 1912, l, 31; and *Dandy, W. E.*, and *Blackfan, K. D.*, Am. Jour. Dis. Child., 1914, viii, 406; 1917, xiv, 424.

[2] For information concerning cerebrospinal fluid, see *Boyd, W.*, Physiology and pathology of the cerebrospinal fluid, New York, 1920; and *Levinson, A.*, Cerebrospinal fluid in health and in disease, St. Louis, 1919; also *Mott, F. W.*, Lectures on the cerebrospinal fluid, Lancet, 1910, ii, 1, 79; and *Weed, L. H.*, Theories of drainage of cerebrospinal fluid, Jour. Med. Research, 1914–15, N. S. xxvi, 21; The cerebrospinal fluid, Physiol. Reviews, 1922, ii, 171 (bibl.).

The distention, especially of the lateral ventricles, may be so great that the brain tissue over the vertex is crowded up into a thin layer beneath the dura mater, or it may be entirely destroyed. When the dilatation of the ventricles is considerable, the convolutions are flattened and may be almost entirely obliterated. The skull bones may be thin and bulging over the forehead and vertex; the fontanelles and sutures widely open. The ependyma in these cases is usually thick and rough, but it may be softened, and the blood-vessels may be dilated. The basal portions of the brain may be flattened, but are usually much less affected than the upper portions. The brain tissue is usually soft and anemic. In advanced cases there is often atrophy of the lateral columns.

2. Secondary Hydrocephalus.—This may occur in children and adults, and may be a result of epidemic cerebrospinal meningitis, of acute meningitis, or of chronic meningitis, either simple or tuberculous. It sometimes occurs in chronic alcoholic poisoning and in general paralysis of the insane. It may be caused by the presence of echinococcus in the ventricles, blocking the free outflow of cerebrospinal fluid. The presence of a tumor may exert sufficient pressure to prevent the

Fig. 775.—Congenital Hydrocephalus in Child. About half natural size.
a, *a*, Dilated lateral ventricles; b, cornua, unequally dilated; *c*, third ventricle; *d*, middle commissure.

outflow of the secretion of the ependymal cells; and, in rare instances, obstruction may be due to the crowding of the pons and posterior portion of the cerebellum into the foramen magnum, as a result either of rapidly increasing intracerebral pressure or of the incautious and rapid removal of large quantities of fluid by lumbar puncture. The amount of dilatation of the ventricles varies greatly in these cases, but it is never so great as in congenital hydrocephalus, and is not accompanied by the changes in the shape of the skull which form so prominent a feature in the latter disease, since the bones are firmer and the sutures united. In this form of chronic hydrocephalus the changes in the ependyma above described are usually more or less well marked, and they may be associated with the production of fibrin and pus.

3. Primary Hydrocephalus in Adults.—The conditions leading to this form of lesion are not understood. It is apt to occur in persons

over thirty years of age. Sometimes one, sometimes both lateral ventricles are dilated. The dilatation is usually moderate, sometimes very slight and never so great as in congenital hydrocephalus. The ventricles usually contain transparent serum, and the ependyma is thickened and roughened. A chronic leptomeningitis is not infrequent. In some cases the hydrocephalus is the only lesion found to account for the death of the patient.[1]

TUMORS.

New formations of connective tissue in the ependyma, although usually diffuse, may be circumscribed and form small, projecting connective-tissue nodules which may be classed among the **fibromata.** Small fibromata are sometimes detached from the walls of the ventricles and lie free in the cavity. Small **lipomata, angiomata, cystic sarcomata,**[2] **"peritheliomata,"**[3] and **gliomata**[4] occur rarely, and may arise from the walls of the ventricle or the plexus. **Chondromata** and **angiomata** may occur in the choroid plexus, the latter sometimes being as large as a hen's egg. The choroid plexus is not infrequently the seat of transparent **cysts,** usually of small size; they may contain clear fluid, colloid material, droplets of fat, or calcareous particles. The cysts have no special pathological significance. **Dermoid cysts** containing hairs have been found in the ventricles.[5]

Very rarely papillary **epithelial tumors** arise from the cells covering the choroid plexus, and cysts containing mucus may be found in them, as well as epithelial pearls. They are not malignant, as a rule, and remain confined to the ventricular cavity.[6]

The calcareous bodies called **"brain sand"** (Fig. 762), which are aggregations of particles of carbonate and phosphate of lime with a small amount of phosphate of ammonia and magnesium mixed with more or less organic matter, occur frequently in the choroid plexus, and **corpora amylacea** may occur here and beneath the ependyma.

PARASITES.

Cysticercus[7] and **echinococcus** cysts are sometimes attached to the walls of the ventricles or may be free in their cavities. In the latter case, echinococcus may, by obstructing the flow of fluid from the ventricles, incite hydrocephalus, or by pressure may cause glycosuria. **Blastomycetes** have been found in the ventricles and in cysts in the brain substance.[8]

[1] For theories of causation of hydrocephalus, see *Weber, L. W.*, Arch. f. Psychiat., 1906, xli, 64. For studies on the cerebrospinal fluid, including its relation to hydrocephalus, see *Cushing, H., Weed, L. H.*, and *Wegefarth, P.*, Jour. Med. Research, 1914–15, N. S. xxvi, 1.

[2] *Hirsch, K.*, Berl. klin. Wchnschr., 1892, xxix, 727, 751.

[3] *Wätzold*, Zieglers Beitr., 1905, xxxviii, 388.

[4] *Mallory, F. B.*, Jour. Med. Research, 1902, iii, 1; *Link*, Zieglers Beitr., 1903, xxxiii, 98.

[5] *Bostroem*, Centralbl. f. allg. Path., 1897, viii, 1 (bibl.).

[6] *Saxer*, Zieglers Beitr., 1902, xxxii, 276; and *Hart*, Arch. f. Psychiat., 1910, xlvii, 739.

[7] *Kocher, R. A.*, Zieglers Beitr., 1911, l, 338 (bibl); and *Sato, T.*, Deutsch. Ztschr. f. Nervenh., 1904, xxvii, 24.

[8] *v. Hansemann*, Verhandl. d. deutsch. path. Gesellsch., 1906, ix, 21.

The Brain and Spinal Cord.

Malformations of the Brain.

Cyclopia.—This malformation consists in an arrest of development affecting the cerebrum, which, instead of separating into two hemispheres, remains single, with one ventricle, the rudiments of the eyes usually uniting to form one eye (Fig. 187). This single eye is in the middle of the face, near the place of the root of the nose, in a single orbit. Over this is an irregular body representing the nose. The rest of the face is well formed. The eyeball may be wanting entirely, or there may be two eyes joined together, or, more seldom, two separate eyes. The orbit is surrounded by rudiments of four eyelids. The frontal bone is single, the nasal bones are undeveloped; the ethmoid, vomer, and turbinate bones are absent. The optic nerve is double, single, or absent. There may be hydrocephalus. Such children are incapable of prolonged existence.

Anencephalia.—This malformation may be of various degrees. The brain may be entirely absent, the base of the cranium being covered with a thick membrane, into which the nerves pass. The membranes may form a sort of cyst containing blood and serum or portions of brain. Of the cranial bones, only those which form the base of the skull are present (*acrania*). The scalp is usually partly or entirely absent over the opening in the skull; the eyes are prominent, and the forehead slopes sharply backward. This malformation may occur in otherwise well-developed children.

Hydrocephalus.—This lesion has been already considered above. It is probable that in some cases *hydrocephalus internus* is due to a primary *partial anencephalia*, and that the accumulation of fluid is of secondary occurrence. In rare cases, only part of one lateral ventricle is hydrocephalic, giving to the head a protuberance on one side. The viability of the fetus depends upon the degree of the hydrocephalus. *Hydrocephalus externus* is an accumulation of serum beneath the pia mater, or, according to some authors, between the pia and arachnoid membrane. It causes dilatation of the cranium and compression of the brain. It is of very rare occurrence, and may also be secondary to partial anencephalia.

Cephalocele, or Brain Hernia.—When abnormal openings exist in the skull from malformation, the contents of the cerebral cavity are apt to protrude in the form of larger or smaller sacs. This may occur in cases of well-marked anencephalia or in cases in which the brain is well developed. The protruding sac formed of the meninges may or may not be covered with skin. If the contents of the sac are simply fluid, the lesion is called *hydromeningocele;* if composed of brain substance, *encephalocele* (Fig. 191); if the sac contain both fluid and brain substance, it is called *hydrencephalocele.* The sacs may be very small or as large as a child's head. They may protrude from the top of the skull in acrania. They most frequently protrude through openings in the occipital bone, often hanging down in large sacs upon the neck; also at the root of the nose, along the line of the sutures, at the base of the skull, and elsewhere.

Microcephalia.—This is an abnormally small size of the brain, with a correspondingly small cranium. The diminution in size affects principally the cerebral hemispheres, though the other parts of the brain are also small. Thus the cerebellum may be of extremely small size. The cord may be smaller than normal, in which case the diminution in size is apt to show a direct dependence upon the cerebral lesions, the direct and the crossed pyramidal tracts being most affected. There may also be present imperfect development of the posterior columns and of the direct cerebellar tracts. The convolutions are few and simple, the cavities often dilated with serum; on the membranes there may be traces of inflammation. The cranium is small, the face large, the rest of the body small. This malformation is in some cases caused by inflammation or dropsy of the brain during fetal life. It is endemic in some countries, and may affect a number of persons in the same family; but single cases often occur. The fetus is viable. Absence or incomplete development of portions of the brain may occur, not only in idiots, but in persons whose minds are perfect.[1]

[1] For a general consideration of malformations of the central nervous system, consult *Thoma*, Pathology and Pathological Anatomy, English translation, vo . i, 206 et seq.; and *Ernst, P.*, Schwalbe, Die Morphologie der Missbildungen des Menschen u. der Tiere, Jena, 1909, vol. iii, part 2, p. 67.

Malformations of the Spinal Cord.

The malformations of the spinal cord may be conveniently classed as follows:

I. Congenital Deformities Associated with Monstrosities, and Incompatible with Extra-uterine Life.

These may be divided into:

1. *Amyelia,* or absence of the spinal cord. This is almost invariably associated with absence of the brain.

2. *Atelomyelia,* or partial development of the spinal cord. This is often seen in the anencephalous or acephalic monsters, where, corresponding to the incompletely developed brain, there may be various degrees of defective development of the cord.

3. *Diastematomyelia,* a condition in which a portion or the whole of the cord is split into two lateral halves. Each half of the cord is developed in its own membranes and gives rise to its own nerve roots. There may be union at one or more points to form a single cord.

4. *Diplomyelia,* or a formation of two spinal cords—a duplication of the spinal cord. This happens in the various kinds of double monsters.

Fig. 776.—Hydromyelia.

In the section from which this drawing was made, the epithelial cells surrounding the dilated central canal were well preserved.

II. Minor Congenital Malformations not Inconsistent with the Maintenance of Life.

1. *Hydrorrhachis interna* is a defective closure or arrangement of the divisions of the primary fetal central canal often resulting in the dilatation of the central canal by fluid (*Hydromyelia,* Fig. 776). This dilatation may be moderate, or so extreme that but little of the substance of the cord is left as a thin shell around the central cavity. When they have not been destroyed by atrophy, epithelial cells may be found lining the cavity.

This condition may be accidentally found after death. Its presence may also be indicated by its association with spina bifida.[1]

2. *Heterotopia,* or misplacement of the substances of the cord.

(*a*) There may be misplaced portions of the gray matter.

(*b*) Portions of the white matter may be arranged in an unusual manner.

3. *Anomalies of the Spinal Nerve Roots.*

4. *Asymmetries of the Spinal Cord.*

III. Malformations of the Spinal Cord Acquired during Extrauterine Life or Secondary to Defective Development in Other Parts of the Body.

1. Distortions following other cord lesions.

2. Asymmetry of the cord due to arrested development after birth or to secondary

[1] Under this subdivision the condition known as *hydrorrhachis externa* may be conveniently alluded to, which consists in an abnormal congenital accumulation of fluid between the meninges of the cord, causing more or less diminution in the volume of the latter.

atrophy of portions of the cord in association with defective development or absence of some other part of the body.

3. Asymmetry of the cord with congenital defects of the extremities or muscles, such as intrauterine or other amputations, clubfoot, etc.

4. Variations in the volume of the cord as a whole.

False Heterotopia.—Congenital displacement of the gray or white matter of the spinal cord—*heterotopia*—has been frequently described. It has been shown,[1] however, that in a large proportion of cases the so-called heterotopia is an artefact (Fig. 777) and has been caused by bruises or careless handling of the cord during its removal from the body or in the process of examination or hardening.

Spina Bifida.—In the majority of cases hydrorrhachis is accompanied by a more or less complete lack of closure of the spinal canal posteriorly, so that the collections of fluid within may pouch outward through the opening in the form of a sac. The sac may be covered by skin, or this may be absent, either from the beginning or as a result of thinning and rupture. The walls of the sac may consist of the dura mater and the pia mater, or, in cases of hydrorrhachis externa, of the dura mater alone. When both are present they are usually more or less fused together. Inside of the membranes of the sac there may be a shell of distended nerve tissue of the cord; or the spinal cord may be split posteriorly and the sides crowded sideways; or there may be a rudimentary fragment of the cord suspended in the sac or attached to the walls; or the cord may be but little changed and remain inside the spinal canal. The openings in the spinal canal may be due to the complete or partial absence of the vertebral arches, or more rarely the sac may protrude through openings between the completely formed arches. Spina bifida most frequently occurs in the lumbar and sacral regions, but it may occur in the dorsal or cervical regions, or the canal may be open over its entire length. Very rarely it is open on the anterior surface. The protruding sac may be very small or as large as a child's head. The fluid in the sac is usually clear, but may be turbid from flocculi of degenerated nerve tissue.[2]

Fig. 777.—False Heterotopia. Section, from Cervical Region of Spinal Cord.

Showing artificial displacement of the structures by an experimental bruise ("false heterotopia") after the removal of the cord from the body. (Van Gieson.)

SACRAL TUMORS AND CYSTS.[3]

In addition to the malformations of the lower end of the spinal cord, a variety of types of complex congenital tumors are seen in the region of the sacrum and coccyx. The majority are developed in connection with developmental malformations about the postanal gut and neurenteric canal, for during embryonic life there is a connection between the spinal canal and the intestine in this region. Some of the tumors are, however, evidently of bigerminal origin, for they are made up of fragments of another fetus.[4] Others are found to contain

[1] For a study of artefacts of the nervous system, see *Van Gieson, I.*, New York Med. Jour., 1892, vi, 337, 365, 421.

[2] For further anatomical details, see the standard text-books on surgery, and *Lecène, Proust,* and *Tixier,* Précis de pathologie chirurgicale, Paris, 1909.

[3] *Keen* and *Coplin,* Surg., Gynec., and Obst., 1906, iii, 661 (bibl.); *Borst,* Centralbl. f. allg. Path., 1898, ix, 449 (good bibl).; *Prym,* Frankfurt. Ztschr. f. Path., 1912, ix, 1 (neuroepithelioma); *Nakayama,* Arch. f. Entwcklngsmechn. d. Organ., 1905, xix, 475 (teratoid tumors); *Hagen, W.,* Beitr. z. klin. Chir. (Bruns), 1904, xlii, 646; *Englemann,* Arch. f. klin. Chir. (Langenbeck), 1903–1904, lxxii, 942; *Schramm,* Wien. klin. Wchnschr., 1910, xxiii, 55 (complex tumors); *Markoe, F. H.,* and *Schley, W. S.,* Am. Jour Med. Sc., 1902, cxxiii, 820; *Mallory, F. B.,* Jour. Med. Research, 1902, N. S. iii, 1.

[4] For illustrations, see *Bland-Sutton,* Tumours: Innocent and Malignant, 5th ed., New York, 1917, pp. 425, 443, and 444.

nerves, parts of eyes, kidney, thyroid, mamma, intestine, and other adult tissues. A less complex type is the cystosarcoma, which is composed of mixtures of sarcomatous or embryonic connective tissue, embedded in

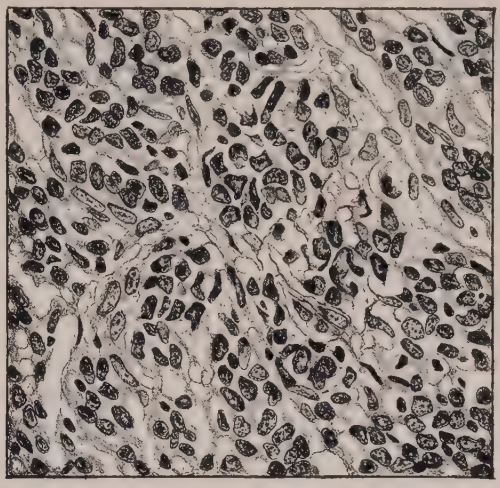


FIG. 778.—NEUROEPITHELIOMA FROM TUMOR OF SACRUM.

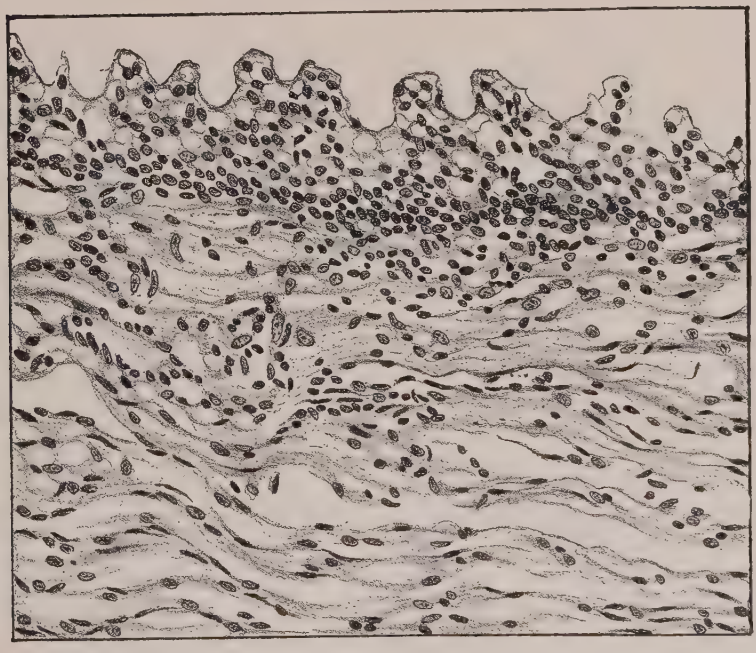


FIG. 779.—LINING OF WALL OF CYST FROM SACRAL REGION.

which are epithelial cysts. Dermoid tumors and lymphangiomata are also found. Of the simpler tumor types lipoma, chondroma, neuroblastoma (Fig. 778), and the ordinary types of sarcoma have been de-

scribed. In addition to these tumors, remnants of the neurenteric canal may be found quite frequently in the form of the so-called postanal dimples, shallow depressions over the tip of the coccyx. These dimples may be deep so that a sinus is formed lined by skin containing hair, sweat and sebaceous glands, the so-called pilonidal sinus. The tissues may become infected, and all the skin structures be destroyed by the suppurative process. In some instances the fistulæ may connect with the spinal canal and be lined with cylindrical or ciliated epithelium. Closed cysts lined with either squamous or columnar epithelium are also found in this region (Fig. 779).

CONGENITAL DISEASES OF THE BRAIN.

Mental Deficiency.

Three types of mental deficiency are generally recognized which grade into each other and are distinguished only by arbitrary divisions.

A moron represents the highest class. Such persons are merely children mentally, and the examination of the central nervous system shows no constant anatomical differences from the normal. The brain weight may equal or exceed that of the most intelligent of the human race.

The imbecile is the next grade and in some instances the brain anatomically is normal; in others the brain is smaller and may show some increase in the neuroglia; or congenital defects such as porencephalus, hydrocephalus may be present or other changes many of them probably due to vascular or inflammatory lesions at an early age. In some cases paralysis may exist, either monoplegic or diplegic, due often to hemorrhages following prolonged and difficult labor or instrumental trauma. These children may have a perfectly normal mentality or may grade through severe imbecility into the lowest type, depending upon the site and extent of the lesion. Some imbeciles undoubtedly owe their condition to congenital syphilis and it has been recently recognized that there may be correlated with this infection a type of juvenile general paralysis in those who are ordinarily classed as imbeciles.

By some writers the Mongolian type of idiocy is considered to belong in the syphilitic group[1] but in general the opinion is that syphilis when present is only a coincident process and has no etiological relationship to the disease. Cases of this type of idiocy are easily recognized by their small size, Mongolian features, furrowed tongue (lingua scrotalis), short stubby fingers. Enlargement of the sella turcica has been noted.[2] Constant brain lesions have not been described though the organ is small and the modelling rudimentary. Malformations of the face, ears, palate, and genital organs are frequent. The basal metabolism is not lowered which differentiates the patients from cretins or congenital myxœdemics.[3]

[1] *Stevens, H. C.*, Jour. Am. Med. Assn., 1915, lxiv, 1636.

[2] *Timme, W.*, Arch. Neurol. & Psychiat., 1921, v, 568.

[3] For Mongolian idiocy, see review of recent literature, Am. Jour. Dis. of Child., 1919, xviii, 146–148; *Tumpeer, I. H.*, Jour. Am. Med. Assn., 1922, lxxix, 14.

Another well marked group of idiots are the cretins whose condition is due to atrophy or abnormal functional activity of the thyroid gland (see pp. 480 and 1064). The brain is small and the ventricles may be dilated. The exhibition of thyroid substance in young cretins sometimes produces considerable intellectual improvement showing that the brain is not seriously altered but in others the amentia persists unimproved.

In idiots not of the Mongolian or cretin type, the most frequent lesion is atrophy of the brain substance following vascular changes occurring either previous to or following birth. Meningeal hemorrhage is commonly the primary lesion in these cases. The site of the hemorrhage determines to a certain extent the symptoms of the patient. If the motor areas are involved, paralyses of various types are to be expected. A great thickening of the dura, in the earlier stages of the hemorrhagic type and later becoming fibrous (see pp. 1113, 1117, 1129) may be a dominant lesion. This new formation may compress the brain substance simply, or may cause extensive pressure atrophy. If the vascular lesion extends to the vessels supplying a definite portion of the brain, atrophy often accompanied by extensive sclerosis may result.

Another type of lesion seen in the brains of idiots is the hydrocephalic form, either primary or secondary (see p. 1129). Very extensive destruction of the brain substance may result, occasionally the cerebral cortex being reduced so that its thickness may not exceed a millimeter.

In secondary hydrocephalus due to inflammatory lesions or tumors, the atrophy of the brain is not as great, but owing to the rapidity of the development of the pressure the life of the patient is apt to be short, even though complete amentia may not have been produced. Accompanying the hydrocephalus may be independent congenital malformations with diminished size or absence of portions of the whole cerebrum, of one hemisphere, the corpus callosum, or of the cerebellum. In other instances, especially in the microcephalic idiots, there may be no striking gross pathological changes in the brain. The organ may simply present a condition of arrested development with the persistence of fetal morphology, both as regards the naked eye appearance of the organ and its microscopical features. Usually, however, detailed study of these brains reveals changes of an inflammatory nature suggesting that prenatal infections or toxic agents may play a part in the etiology. There may be a compensatory hydrocephalus or a thickening of the skull in these cases of small brains, and occasionally an external hydrocephalus accompanies agenesis of the cortex. Such collections of fluids are likewise apt to be present together with skull thickening in idiots with porencephaly and microgyria.

While, as a rule, alterations in the size and shape of the skull are regular external accompaniments of idiocy, a large number of other "stigmata of degeneration" are often present. The most varied defects of the face such as hare-lip, cleft palate, deformities of the ears, and of the extremities are frequently seen. Mental deficiency has even been noted in connection with hemihypertrophy of the body, which must be regarded as a form of asymmetry dating back to an early embryonic stage.

Epilepsy.

The nervous systems of epileptics present no uniform pathological changes. In fact, there are many cases in which careful macroscopic as well as microscopic examinations of the brains reveal nothing of unusual appearance. On the other hand, there are other cases which present all degrees of pathological changes ranging from mere simple degeneration of the nervous tissue and replacement by neurolgia to complete loss of one or more lobes and even of an entire hemisphere. The changes often reported in medical literature, i.e., hemorrhages, cloudy swelling, chromatolysis, and neuronophagy, may be accounted for by the injuries received during convulsions, and by the immediate causes of death in these cases, such as status epilepticus or an acute infection like pneumonia. From the viewpoint of pathology, epilepsy cannot be regarded as the result of a distinct anatomical lesion.

Tuberous Cerebral Sclerosis.

This is a congenital cerebral lesion characterized by the presence of tumor-like masses of glia tissue in various portions of the brain, from which varying degrees of idiocy or epilepsy result.[1] In addition to the lesions in the brain, tumors of the type of adenoma sebaceum are often found in the skin; in a considerable number of cases tumors are present also in the heart and in the kidney. Most of the patients die early.

The gliomatous changes involve individual convolutions or groups of convolutions, and may give rise to small tumors in the lateral ventricles and occasionally on the dura of the brain and cord. Heterotopic islands of cortical material may be present in the brain substance. Microscopically, the growth is a gliosis differing from the ordinary type by the presence of very large irregular cells whose nature has not yet been established. Some of these resemble the cells of the glia; others resemble ganglion cells. The sclerotic areas contain very few nerve fibers. In the fresh condition, the new growth of tissue is recognizable by the fact that it is lighter in color than the rest of the brain and is much firmer. Owing to this greater density the mass may project somewhat above the general level of the convolutions. There is, however, no sharp boundary between the normal brain and the gliosis.

The cardiac tumors are rhabdomyomata composed of embryonal muscle cells.[2] The skin lesions are those of adenoma sebaceum (Fig. 263, page 462), which are composed of alveoli filled with epithelial cells resembling those of the sebaceous glands. Usually the tumors are small, but they may measure several centimeters in diameter.

The kidney tumors are present in about 25 per cent. of the cases, and may be of the type of hypernephromata or sarcomata, but they may also be exceedingly complex, containing striated muscle fibers, epithelial tubules, and other structures evidently due to some congenital displacement.[3]

[1] *Neurath, R.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1908, xii, 732 (bibl.); *Bundschuh, E.*, Zieglers Beitr., 1912, liv, 278 (bibl.).

[2] *Wolbach, S. B.*, Jour. Med. Research, 1907, N. S. xi, 495.

[3] *Kirpicznik, J.*, Virchows Arch., 1910, ccii, 358.

Amaurotic Family Idiocy (Tay-Sachs Disease).

This is a type of congenital affection of the brain causing idiocy, muscular weakness, and a rapidly developing blindness. The retinal macula shows a cherry-red central spot surrounded by a pale area, a condition which is of importance in diagnosis during life. Death occurs usually within two years of the beginning of the disease. A number of children in the same family are apt to be affected; and all but one of the reported cases have been in Hebrews.

Grossly, the brain is poorly developed, the tissue is firm and hard. Microscopically, there is a widespread degeneration of the ganglion cells of the brain, cord, and spinal ganglia. The cells show a swelling of the cytoplasm and dendrites, and alteration and, ultimately, disappearance of the Nissl bodies, with destruction of the cell fibrils.[1] Finally, the fiber tracts in brain and cord degenerate. Inflammatory and vascular lesions are not present; nor do the tissues show evidence of syphilitic infection.

A juvenile type not limited to the Hebrew race, and occurring in children of from six to fourteen years, has been described.[2] The macular spot is not found in this form and an optic atrophy only is present. The ganglion cells are not so completely altered as in the infantile group; the cortex and spinal cord are not much changed. The retina shows loss of the rods and cones.

INJURIES OF THE BRAIN.[3]

The brain may be wounded directly by a foreign body, or indirectly by fragments of bone driven into it, or it may be lacerated by severe contusion without fracture or solution of continuity of the skull. Very severe injuries of the brain are often caused in parts of the organ remote from the seat of violence; thus blows on the skull frequently cause laceration of the brain on the opposite side. This is called injury by *contrecoup*. It is very difficult to estimate the degree of injury which must cause death, since some persons die from slight, and others recover from very severe, wounds of the brain. In incised wounds of the brain more or less hemorrhage occurs at the seat of lesion, and the brain tissue in the vicinity soon undergoes degenerative changes. These may be comparatively slight or extensive. Inflammatory reaction may occur in the vicinity, and the adjacent brain tissue, as well as the hemorrhagic and degenerated area, may become infiltrated with pus cells. After a time the injured and degenerated area may become surrounded by new-formed connective tissue, and the decomposed extravasated blood and detritus of brain tissue, more or less fatty, may be absorbed. In this way the part heals, leaving a somewhat pigmented cicatrix. The healing is in most cases very slow. The pia mater may participate to a marked degree in the inflammatory healing process.

After wounds which involve the removal of portions of the cranial

[1] For details, see *Sachs, B.*, Jour. Nerv. and Ment. Dis., 1903, xxx, 1; *Sachs, B.*, and *Strauss, I.*, Jour. Exper. Med., 1910, xii, 685; *Bing*, Ergebn. d. inn. Med. u. Kinderh., 1909, iv, 82.

[2] *Spielmeyer, W.*, Nissl and Alzheimer, Histologische und histopathologische Arbeiten, Jena, 1908, ii, 193 (bibl.).

[3] For detailed discussions, see *Macklin, C. C.*, and *Macklin, M. T.*, study of brain repair in rat by use of trypan blue, Arch. Neurol. and Psychiat., 1920, iii, 353; and *Essick, C. R.*, Pathology of experimental traumatic abscess of the brain, Arch. Neurol. and Psychiat., 1919, i, 673.

bones, it is not uncommon after a few days to see a bleeding fungous mass projecting through the opening. This mass, sometimes wrongly called hernia cerebri, consists of degenerated brain tissue, blood, and granulation tissue, with more or less pus. The brain tissue below it is degenerated, soft, broken down, and purulent, and there is often abscess in the adjacent brain tissue. Such wounds may finally heal by the absorption of the broken-down brain tissue and blood, and its replacement by granulation tissue.

Lacerations of the brain tissue without fracture may appear shortly after the injury as simple, more or less circumscribed areas of capillary hemorrhage; the brain tissue about these may degenerate, pus may form, and abscesses be developed; or the degenerated and lacerated tissue may be gradually replaced by granulation tissue which finally forms a cicatrix. The process of degeneration and softening and of healing in such lacerations of brain tissue may occur very slowly indeed, even occupying years, and not infrequently the degenerative changes are very extensive and progressive. In many cases, of course, the injury is so extensive, or involves such important parts of the organ, that very little or no inflammatory or degenerative change takes place before death.

INJURIES OF THE CORD.

The spinal cord may be compressed or lacerated by penetrating wounds, by fracture or dislocation of the vertebræ, or by concussion without injury to the vertebræ. The spinal cord is found simply disintegrated, or there may be much hemorrhage and the disintegrated nerve tissue be mixed with blood. If life continue, the nerve elements may degenerate; Gluge's corpuscles and free fat droplets may form; blood pigments may be formed; and when inflammation supervenes more or less pus may be intermingled with the degenerated material. There may be marked changes in the minute structure of the cord, without any change being evident to the naked eye.

INJURIES OF THE NERVES.

The secondary effects of injuries to nerves are described in the section on degenerations following injury. After amputation of a limb, there often occur swellings of the peripheral ends of the divided nerve trunks. These bulbous ends are called false or amputation neuromata. Usually they contain a considerable proportion of nerve fibers mingled with scar tissue, the relative amounts varying in different specimens.

HYPERTROPHY AND ATROPHY OF THE BRAIN.

True Hypertrophy of the brain is rare, and probably always congenital. An increase in the size of the brain from the proliferation of the neuroglia sometimes occurs in children either before or after birth, less frequently in youths, and very seldom in adults. The white substance of the hemispheres is increased in amount. If it takes place before the ossification of the cranium, the bones are separated at the sutures and fontanelles; if after this, the inner table of the skull may be eroded and

thinned. When the cranium is opened the dura mater appears tense and anemic, the convolutions of the brain are flattened, the brain substance is firm and anemic, the ventricles are small, the ganglia and cerebellum are either of normal size or compressed.

The disease is usually very chronic, and destroys life with symptoms of compression of the brain. There may, however, be acute exacerbations.

Atrophy.—This may occur as a senile change, or, in chronic alcohol, opium, or lead poisoning, in paresis, and in chronic meningitis, or from local interference with the circulation. In children who are much reduced by chronic diseases atrophy of the brain may accompany atrophy of the rest of the body.

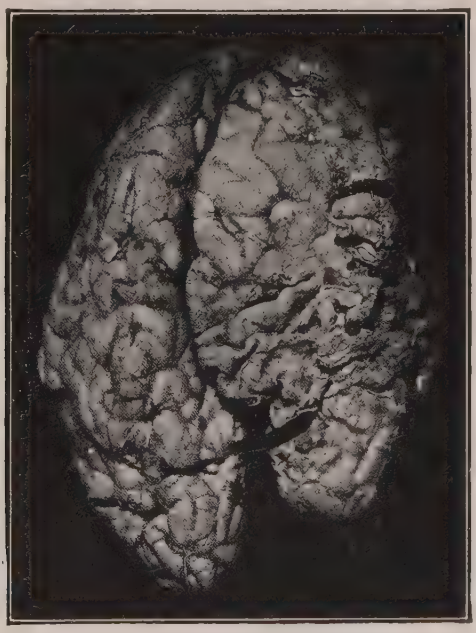


FIG. 780.—ATROPHY OF A CIRCUMSCRIBED PORTION OF BRAIN CONVOLUTIONS IN A CHILD. From a lesion of the corresponding blood-vessels.

The atrophy affects principally the cerebral hemispheres, and may be uniform or more marked in some parts than in others, involving the whole of a hemisphere or of a lobe or only single convolutions or groups of these (Fig. 780). The convolutions are small, the sulci broad, the ventricles usually dilated, the brain tissue is firm, the gray matter discolored, the white substance grayish in color; the blood-vessels may be dilated. The basal ganglia may be small. Serum accumulates in the pia mater and in the ventricles; the pia mater, and often the skull, become thickened; the brain tissue may be edematous or contain small hemorrhages. The nerve elements of the brain tissue are those most involved in the atrophy, the diminished areas being usually harder and firmer than normal. The neuroglia is usually increased.

PIGMENTATION OF THE BRAIN.

This may occur in any portion of the brain or its meninges from the decomposition of extravasated blood. In persons affected by malaria the gray matter of the brain has sometimes a dark or even blackish appearance. This color is due to the presence of black pigment granules within the capillary blood-vessels. The obstruction to the vessels by masses of these pigment granules may cause capillary apoplexies. The pigment may also be found in the walls and in the lumina of the vessels of the pia mater. Pigmentation of the brain is seen in ochronosis, also.[1]

Pigment patches of congenital origin are not infrequently seen in the pia mater. They may be due to the presence of branching pigmented cells.[2] Melanosarcomata may develop from such chromatophores.[3]

CIRCULATORY AND VASCULAR CHANGES IN THE BRAIN AND SPINAL CORD

Anatomical Considerations.

In studying the circulatory changes in the brain and cord certain peculiarities in that circulation should be borne in mind. The vessels which nourish the brain arise from a remarkable anastomosis of large arterial trunks at its base, known as the circle of Willis (see diagram, Fig. 781). From this "circle" pass off to each hemisphere three main branches—the anterior, the middle, and the posterior cerebral. These arteries ramify in the pia, where they anastomose freely. From this anastomosis small branches are given off which penetrate the brain substance, the shorter breaking up into capillaries in the gray matter, the longer passing to the underlying white matter. After entering the cortex there is no further anastomosis, the capillaries of a cortical artery passing directly over into a venous system of capillaries without communicating with capillaries of other arteries. They are thus "terminal arteries." In addition to these arteries, which supply the hemispheres, branches from the circle of Willis are distributed to the basal ganglia. These arteries are much larger than those which pass from the pia into the cortex, and beyond the circle of Willis do not form anastomoses with one another. Thus it is that occlusions of the arteries supplying the basal ganglia are much more serious, aside from the importance of the parts involved, than of those passing to the cortex.

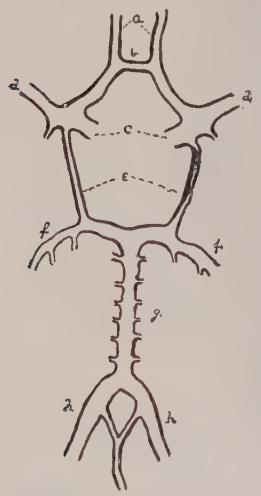


FIG. 781.—DIAGRAM OF THE CIRCLE OF WILLIS AND ASSOCIATED VESSELS.

a, Anterior cerebral; *b*, anterior communicating; *c*, internal carotids; *d*, middle cerebral; *e*, posterior communicating; *f*, posterior cerebral; *g*, basil- , *h*, vertebral.

Three main arteries furnish blood to the cord: the anterior spinal, lying along the opening of the anterior median fissure, and two posterior spinal, lying near the entrances of the posterior roots. Branches of these arteries anastomose in the pia, and from this pial network branches pass directly into the substance of the cord. The largest, a branch of the anterior spinal, passes into the pia of the anterior fissure, and, penetrating the cord, is distributed to the gray matter of the anterior horn, and to the median gray matter as far back as Clarke's column. Smaller arteries from the posterior spinal supply the posterior regions of the cord. These arteries, like those in the brain, are terminal in the sense that, while anastomosing freely in the pia, after penetrating the substance of the cord they form no further anastomoses.

[1] *Pick*, Berl. klin. Wchnschr., 1906, xliii, 478.
[2] *Virchow*, Virchows Arch., 1859, xvi, 180.
[3] *Stoerk*, Wien. klin. Wchnschr., 1904, xvii, 184; *Pick*, Berl. klin. Wchnschr., 1906, xliii, 884.

In structure the vessels of the brain differ from those of the rest of the body sufficiently to warrant mention here. The intima and the elastic membrane are much closer to each other than in the other vessels; longitudinal elastic fibers are very scarce; and the internal elastic lamina is very much thicker in the cerebral vessels of large caliber than elsewhere. At the point of contact between the muscular layers and the adventitia there is, however, in the larger vessels, especially the vertebral and the basilar, a layer of coarse elastic fibers running longitudinally. There are no vasa vasorum in the larger cerebral arteries. The smaller vessels are composed solely of endothelium and elastic tissue with a thin elastic layer between them and occasional muscle fibers; the last are absent from the capillaries. The small veins possess an elastic lamina not present in the larger, so that they can not be distinguished from small arteries. About the vessels are lymph-spaces, called the Virchow-Robin lymph-spaces, which may contain embolic tumor cells or leucocytes in inflammatory lesions of the brain. These Virchow-Robin lymph-spaces drain into the subarachnoid spaces. Between the vessel and the nerve tissue there is interposed a thin layer of neuroglial tissues, the *perivascular limiting neuroglial membrane.* The great vascularity of the brain in comparison to its bulk, the close relationship of the vessels to the substance, the great importance of the perfect competence of such circulation because of the serious lesions which rapidly follow interference with the blood flow; all these make arteriosclerosis a very much more important phenomenon in the cerebral vessels than in other organs of the body.

Hyperemia and Anemia.

The appearance of the brain tissue after death does not always furnish reliable indications of its blood contents during life, though it is perhaps more to be depended on than the appearance of the meninges.

Some of the more common conditions determining *hyperemia* which are mentioned above as influencing the meninges apply also to the substance of the brain.

Active hyperemia may occur in various inflammatory conditions of the brain. Hyperemia of the brain is quite common in deaths from insolation and after conditions accompanied by acute delirium, such as delirium tremens. **Passive hyperemia** may occur in conditions similar to those which determine congestions in other organs of the body, such as chronic diseases of the heart or lungs. It may be induced by anything which prevents venous return, such as intracranial tumors which compress the sinuses, or by thrombosis.

In sections of hyperemic brains the small blood-points from the cut ends of small vessels are more numerous and conspicuous than under normal conditions, and the brain tissue, particularly the gray matter, may have a diffuse red color. If excessive, the convolutions may be somewhat flattened, the brain tissue and pia mater may be edematous, and the ventricles may contain fluid. The congestion of the vessels may be general or localized.

Anemia of the brain may be either local or general. It may depend upon a general anemia or upon general disturbances of the circulation, such as mitral stenosis or regurgitation; or upon local interference with the arterial blood supply, such as complete or partial obstruction of the

arteries from thrombi, emboli, inflammatory changes, spasmodic contractions, etc., or from tumors, exudations, and blood extravasations pressing upon the vessels from without. In edema of the meninges, and in the presence of internal hydrocephalus, the brain tissue is apt to be anemic. The brain tissue in anemia looks whiter than usual, the contrast between the gray and the white matter is less marked, and the small blood-points usually seen on section from divided vessels may be very inconspicuous or almost entirely absent. Anemia, when local and long continued, leads to softening, with destruction of the ganglion cells and the appearance of fatty and granular cells in the affected area.

Edema.

Edema of the brain tissue may accompany either general or localized hyperemia, or it may accompany anemia, and it seems in most cases, though nor always, to be dependent upon conditions which induce these alterations in the blood contents of the brain, such as sinus thrombosis, brain tumors, etc. It is, perhaps, most common in conditions which determine a passive hyperemia. In some cases of marked impoverishment of the blood a so-called *hydremic edema* of the brain is found. This is not infrequent after death from uremia.

In edema the brain tissue appears unusually wet and shiny. The same underlying condition is apt to determine an exudation into the membranes and ventricles. There is usually considerable distention of the perivascular lymph-spaces.

Marked edema of the brain may exist without brain symptoms. On the other hand, persons may die comatose with no other gross lesion than edema, either with or without edema of the pia mater. This is seen with especial frequency in acute and chronic alcohol poisoning, but may occur under other conditions. A careful microscopical examination of the brain under these conditions will frequently reveal structural lesions of more serious import than the edema. Occasionally edema is seen in very acute cerebrospinal meningococcal infections, when death has occurred before the inflammatory lesions have reached a macroscopic stage.

Under the designation of "serous apoplexy," edema of the brain was formerly considered, in the absence of other lesions, of importance as a cause of death. But increased knowledge has led to the general belief that simple cerebral edema as an independent condition has not the significance formerly ascribed to it, and it should be accepted, if ever, with great reserve as a cause of death.

Hemorrhage.

Hemorrhages in the substance of the brain may be very small and punctate, and are then usually called *capillary hemorrhages;* or they may result in the collection in the brain tissue of masses of blood of consider-

able size, which are called *apoplectic foci* or clots. These forms of hemorrhages may be associated, or a number of capillary hemorrhages may join to form an extensive clot.

Capillary hemorrhages may appear, on section of the brain, like the severed ends of hyperemic blood-vessels, or the tissue about them may be more or less tinged with blood. Microscopically, the perivascular spaces are distended with blood, which may have escaped into them. This is associated with more or less broken-down brain tissue. The hemorrhages may be single, but are frequently multiple, so that the brain tissue is besprinkled with blood-points. Degeneration of the extravasated blood may give rise in later stages to reddish or brown or yellowish circumscribed discoloration of the brain tissue, due to granules and crystals of blood pigment intermingled with broken-down brain tissue, with more or less fatty degeneration of its elements. Capillary hemorrhages may be due to fatty degeneration of the vessels leading to rupture; or the extravasation may be due to diapedesis; or it may depend upon conditions which we do not understand. The hemorrhages frequently occur in the vicinity of apoplectic clots and tumors, and may be due to thrombosis of the veins or of the sinuses of the dura mater; they not infrequently occur in acute encephalitis, in congestive hyperemia, in acute mania, and in delirium tremens; and they may be associated with general diseases, such as scurvy, purpura hæmorrhagica, typhus fever, pyemia, ulcerative endocarditis, etc., and with embolic softening.

The cerebral symptoms which follow serious traumatic injuries to the brain have been illuminated of late by the numerous opportunities afforded for the study of the brains of those who have died from shell explosions, no visible external injuries being found.[1] As a rule, the brain and cord are the only organs affected in persons dying either immediately or some time after exposure to shell shock. In the brains of those who have lived for some time, there are found extreme congestion and an extraordinary number of minute punctiform hemorrhages of the spinal vessels and at the terminations of the small capillaries at the surface of the brain. No large hemorrhages are found, as a rule, and no intracerebral petechiæ. There may be ecchymoses about the large sinuses and the cerebrospinal fluid is almost always blood tinged. Subarachnoid hemorrhages or even complete separation have been noted also. When the disease has existed for some time, degenerative changes in the ganglion cells and in the neuroglia, and secondary degenerations in the fiber tracts of the brain and the columns of the cord can be found.[2]

Apoplectic foci may result from the coalescence of numerous capillary hemorrhages; from injury; or from rupture of diseased arteries, either with or without changes in the blood pressure. Hemorrhages from

[1] For a study of the causes of death from shell shock, see *Mott, F. W.*, Brit. Med. Jour., 1917, ii, 612. See also *Lhermitte, J.*, Ann. de méd., 1917, iv, 294; and *Guillain, G.*, and *Barré, J. A.*, ibid., 1917, v, 598 (bibl.). For an experimental study of the traumatic lesions of the central nervous system, see *Jakob, A.*, Nissl and Alzheimer, Histologische und histopathologische Arbeiten, Jena, 1913, v, 182 (bibl.).

[2] The great force which acts upon the brain may be estimated from the fact that the air pressure following the explosion of a large shell at a distance of 3 meters has been computed to be 1 kilo per square centimeter. If the area of the calvarium be estimated to be roughly 500 square centimeters, this would mean that the skull received a blow of 500 kilos.

injury to the skull may occur as well without as with fracture, and may be situated over the vertex or at the base of the brain. They vary in extent and location, depending upon the character and point of the injury and the size of the vessels involved. The so-called spontaneous hemorrhages, other than those of capillary origin, which give rise to masses of blood and broken-down brain tissue, may vary in size from that of a pea to those occupying a large part of a hemisphere. They are due, in a small proportion of cases, to the rupture of aneurysms, but usually arise from weakening of the walls of the arteries, from arteritis, atheroma, or fatty degeneration. These latter lesions doubtless give rise in most cases to the formation of pseudoaneurysms whose rupture is in so many cases the immediate cause of the hemorrhage. A source of extensive spontaneous hemorrhage may be a softened glioma, which may escape detection unless a careful microscopic examination is made of the brain surrounding the clot. Occasionally infectious thrombi form in the larger cerebral vessels, invade the walls, so that weakening results, and give rise to aneurysm-like dilatations which may ultimately rupture and cause extensive hemorrhages, usually at the base of the brain.

Aneurysms of the cerebral arteries may be as large as a pea or hazelnut, but those most frequently met with and causing apoplexy are usually small—called *miliary aneurysms*—and may be microscopic in size, varying from this up to that of a large pin's head or larger. They may be sacculate or fusiform, and frequently exist in considerable numbers. Encapsulated mural hematomata produced by the rupture of a small vessel or destruction of the external coats by a dissecting aneurysm should not be confused with the true aneurysmal type of lesion. Aneurysms may occur in any of the small arteries of the brain, but are said to be most frequent on the branches of the middle cerebral artery. The statement that the bursting of miliary aneurysms is the exclusive cause of spontaneous apoplectic clots is doubtful.[1]

As to the immediate cause of rupture, either of aneurysms or of otherwise diseased blood-vessels in the brain, we are in many cases entirely ignorant. In some cases it seems to be due to an increased arterial tension in such diseases of the heart as induce this change, as in the cardiac hypertrophy which may accompany some forms of chronic diffuse nephritis; or it may result from unusual exertion or mental excitement.

Hemorrhages most frequently occur in the corpora striata and optic thalami (Fig. 782), and in the brain tissue in their vicinity, and here they are most common in the parts supplied by the branches of the middle cerebral artery. The possibility of hemorrhage in the floor of the fourth ventricle should be borne in mind in investigating cases of sudden death from obscure causes.

Hemorrhages frequently seriously affect other portions of the brain than those immediately supplied by the ruptured vessels. Thus hemor-

[1] For extensive studies on the nature and importance of aneurysms of the cerebral vessels, see *Ellis, A. G.*, Proc. Path. Soc., Philadelphia, 1909, N. S. xii, 197; and *Pick, L.*, Berl. klin. Wchnschr., 1910, xlvii, 325, 382. *Shennan, T.*, Miliary aneurysms in relation to cerebral hemorrhage, Edinburgh Med. Jour., 1915, xv, 245; *Raeder, O. J.*, Repeated multiple minute corticospinal hemorrhages with miliary aneurysms in case of arteriosclerosis, Arch. Neurol. and Psychiat., 1921, v, 270.

rhages in the cortical substance or beneath the pia mater may force their way deep into the brain substance; or, in hemorrhage in the brain substance, the blood may burst into the ventricles[1] or work its way into the intermeningeal space, and, either at the seat of its occurrence or in the situations into which it is forced, may give rise to serious compression of the brain. Portions of the brain containing large extravasations may be enlarged, the tissue anemic from pressure, the convolutions flattened,

FIG. 782.—LARGE HEMORRHAGE IN THE BRAIN. "CEREBRAL APOPLEXY."

The hemorrhage involves the right basal ganglia and adjoining brain tissue. The blood is in both lateral ventricles. The right side of the brain (the upper side in the figure) is pressed out with flattening of the convolutions.

and the surface dry. As the blood is poured out, the brain tissue is usually torn and lacerated, so that the apoplectic clot often consists of detritus of brain tissue intermingled with blood. If, however, the blood is poured out from a single vessel, the brain tissue may be pressed aside, and the greater portion of the mass may consist of blood.

The appearances presented by hemorrhages in the brain vary greatly, depending upon the time which has elapsed since their occurrence. If

[1] *Tilney, F.*, and *Casamajor, L.*, Hemorrhage into the basal cisterns and ventricles, Neurol. Bull., 1918, i, 161.

life continue, the edema which usually soon occurs in the vicinity of the hemorrhage disappears and the clot becomes drier and firmer; gradually the blood undergoes the usual series of changes seen in extravasation; the hemoglobin decomposes, forming granules and crystals of blood pigment; and the blood-cells and fibrin undergo degeneration and absorption; the detritus of brain tissue undergoes fatty or myelinic degeneration, the fatty and other particles being taken up by large phagocytic cells. As these alterations occur the color changes to reddish brown, orange, or yellow, and the adjacent brain tissue may be discolored by imbibition.

Inflammatory reaction may occur in the vicinity, leading either to the formation of a more or less pigmented cicatrix, or to a cyst with yellowish fluid contents and a fibrous, more or less pigmented wall formed of glia and connective tissue, the latter being supplied by the vascular sheaths. The process of degeneration and absorption of the blood and broken-down brain tissue, and their replacement by a cyst or by a cica-

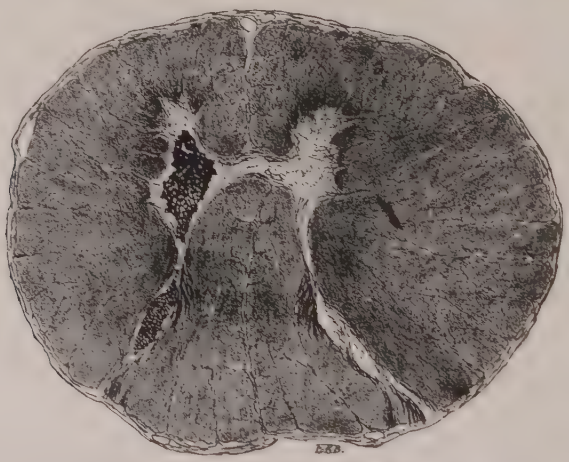


Fig. 783.—Section of the Spinal Cord Showing Hemorrhage into the Gray Matter and Extending Lengthwise of the Cord. (An early phase of hematomyelopore.) This lesion is sometimes called hematomyelia.

trix, is a slow one, and the cysts and cicatrices may resemble those formed at the seat of embolic softening. Not infrequently we find in the brain of a person dead from recent apoplexy the remains of old clots presenting some one of the above-described stages of absorption. The apoplectic cysts and cicatrices persist for a long time after their formation.

Secondary degenerations (page 1165) following hemorrhages depend entirely upon the cells destroyed or the fiber tracts interrupted. Most common are degenerations of the pyramidal tracts from hemorrhages into the sensory-motor region of the cortex, or from hemorrhages into the internal capsule (lenticulostriate artery). Hemorrhages involving the optic centers or the optic fibers lead to degeneration in the optic tracts. Hemorrhages into other portions of the brain, by destroying commissural cells or interrupting their fibers, lead to degeneration of intracranial fiber tracts.

Hemorrhage in the spinal cord is much less frequent than in the brain, but may occur either as capillary apoplexy or as larger apoplectic clots. Capillary hemorrhages, similar in appearance to those of the brain, may occur as the result of injury, or near areas of softening or tumors, or may accompany severe convulsions, as in tetanus. Apoplectic clots, which are comparatively rare in the spinal cord, are usually small, commonly not more than one centimeter in diameter, and are similar in their appearance, and in the changes subsequent to their formation, to those in the brain. They are usually the result of injury, but may occur spontaneously. These so-called spontaneous hemorrhages are undoubtedly in most cases the result of inflammation. They may occur in any acute disease of the cord, and are an especially frequent complication of acute myelitis. Hemorrhage into the cord, occurring in the course of an

FIG. 784.—HEMATOMYELOPORE.

The section shows at one point a cyst-like cavity in the spinal cord, originating in a hemorrhage in the posterior root (see Fig. 783) and extending nearly the entire length of the cord. The cavity is lined by tissue detritus and neuroglia.

acute infectious disease, is probably, as a rule, due to an unrecognized myelitis or acute degeneration. Hemorrhages in the course of a chronic myelitis are not common, and are probably due to a softening dependent on interference with nutrition. Hemorrhages into the cord have been reported in syphilitic myelitis, in syringomyelia, and in tumors of the cord. Gliomata especially are often very vascular, and their thin-walled vessels are subject to rupture. Sometimes, however, hemorrhagic foci are found in the spinal cord without traumatism or evidence of inflammatory change. In caisson disease, hemorrhages may occur secondary to rupture of the capillaries or softening of the cord tissue. They may occur, also, after spinal anesthesia and during delivery.

Larger hemorrhages naturally follow the lines of least resistance, and their long diameter corresponds to that of the cord. To such columnar

hemorrhages, usually traumatic in origin, the name *hematomyelia* has been applied (Fig. 783). The term is being now more properly used to cover the general subject of hemorrhage into the spinal cord.[1]

The smaller capillary hemorrhages may be entirely absorbed. They may, on the other hand, form microscopic sclerotic areas. The larger hemorrhages determine a considerable destruction of tissue. They may be absorbed and replaced by fibrous tissue, or the central area may break down into a fluid or semi-fluid mass of blood and tissue, with a more or less definite fibrous wall (Fig. 784). To these columnar cavities or canals the term *hematomyelopore* has been applied.[2] To a similar condition in which proliferation of the neuroglia is the most marked feature, the name of *false* or *secondary syringomyelia* has been given.

Thrombosis and Embolism.

Thrombi may form in the arteries as a result of any degenerative or inflammatory process in their walls leading to a roughening or death of the intima, or from pressure from without, or they may occur in vessels in whose walls we can detect no primary lesion. The most common causes are atheroma and simple endarteritis. Thrombi may also form around an embolus which does not entirely occlude the vessel. Infectious thrombi may lead to destruction of the walls of the vessel, with consequent hemorrhage.

Emboli of the cerebral arteries most commonly arise from acute or chronic endocarditis or cardiac thrombi; they may arise from aneurysms or atheroma of the aorta, from the carotid or vertebral arteries, or from the pulmonary veins. The materials constituting emboli vary greatly, depending on their mode of origin (page 39). The effects on the brain tissue of emboli and thrombi of the arteries are essentially the same in their main features. In some cases, however, in which large emboli, usually from endocarditis, suddenly block up a large vessel, the individual may die almost instantly without other apparent lesion than the stoppage of the vessel.

In general, the first effect of the occlusion of an artery is to deprive the region to which it is distributed of blood. In arteries whose branches anastomose, the affected area is soon supplied with blood by the establishment of a collateral circulation. In terminal arteries, on the other hand, the blocking of the vessel is followed, as a rule, by degenerative changes and softening in the brain tissue. The appearances which these degenerated areas present vary greatly, depending upon the stage of the degeneration and the amount of blood which may be extravasated. Dense infiltrations of the brain tissue with blood, as in hemorrhagic infarctions from emboli in other parts of the body, do not usually occur, although considerable blood may be extravasated. Areas of softening in which there is little extravasation of blood are usually white or yellow in color, *white or yellow softening*. When much blood is present the proc-

[1] For a case of hemorrhage of the spinal cord, see *Rice, H. W.*, Jour. Am. Med. Assn., 1910, liv, 1783. For bibl. of the subject, see *Lewandowsky, M.*, Handbuch d. Neurologie, Berlin, 1911, ii, 550.

[2] For study of hematomyelopore, see *Van Gieson, I.*, New York Polyclinic, 1897, x, 87.

ess is frequently called *red softening.* Yellow softening is probably often only a secondary stage of the red, resulting from absorption of most of the pigment. The term "white softening" is often used interchangeably with "yellow." It is also applied to that condition into which the latter passes after more complete liquefaction, and after fatty changes have taken place. Young proliferating neuroglia tissue often give a glistening white appearance to the lesion.

The tissue in the affected area gradually softens and may become diffluent. Microscopically, the softened tissue is seen to consist of more or less fluid with broken-down brain tissue, fragments of nerve fibers, drop-

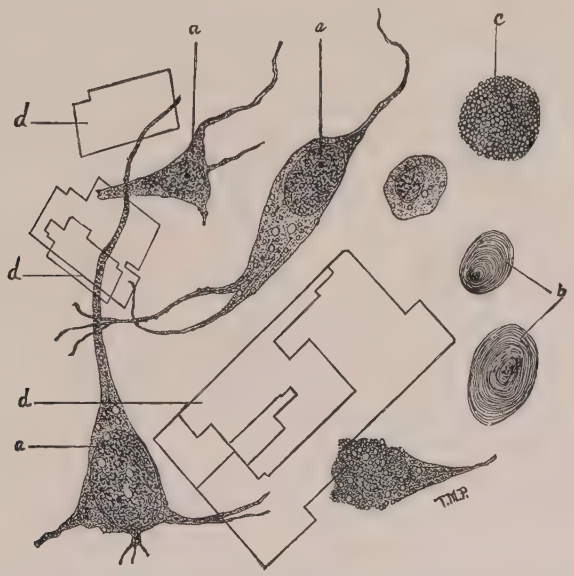


FIG. 785.—DEGENERATED CELLS, CHOLESTERIN CRYSTALS, AND CORPORA AMYLACEA FROM BRAIN TISSUE IN EMBOLIC SOFTENING.

a, Fatty ganglion cells; *b*, corpora amylacea; *c*, cell containing very large number of fat droplets (compound granular or Gluge's corpuscles); *d*, cholesterin crystals.

lets of myelin, nerve cells, shreds of neuroglia tissue and blood-vessels, and red and white blood-cells. The evidence of degeneration is seen in the presence of fat granules and droplets, larger and smaller cells densely crowded with droplets of fat (*Gluge's corpuscles* or *compound granular corpuscles*). Various kinds of cells and cell fragments, more or less granular and fatty, and also corpora amylacea, blood-pigment, fat crystals, and cholesterin crystals, may be found (Fig. 785). The walls of the blood-vessels may also be in a condition of fatty degeneration (Fig. 786). The color of the softened mass will of course depend upon the relative amounts of these elements.

The tissue may remain for a long time in the soft condition, or it may be absorbed and replaced by a connective-tissue cicatrix which may be more or less pigmented; or a wall of connective and glial tissue

may form about it, converting it into a well-defined cyst, with or without pigmented walls; or the mass may dry and form a dense, structureless nodule. Acute inflammatory changes may occur about the dead tissue. In cases of infectious emboli numerous abscesses may be formed in addition to their mechanical action.

Thrombi are most frequent in the internal carotids, less frequent in the middle cerebral, basilar, and vertebrals. They may occur, but still less frequently, in other cerebral arteries. Emboli are most common in the middle cerebral artery, next in the internal carotid, and then in the basilar. The relative frequency with which embolism occurs in the middle cerebral artery is attributable to the directness with which the blood passes into this artery from the heart. The great significance attaching to embolism of the middle cerebral artery is evident when we remember that its branches within the brain are terminal arteries, and are distributed to such important structures as the lenticular and caudate nuclei, the internal capsule, and the optic thalamus.

Fig. 786.—Blood-vessels From an Area of Embolic Softening of Brain.
The walls of the vessels, particularly the endothelial cells, contain fat granules and fat droplets.

Thrombosis and embolism also occur in the vessels of the spinal cord, though less frequently than in those of the brain.

Lesions of the Vessel Walls in the Brain and Cord.

The mural changes in the vessels are not peculiar to the nervous system: the most frequent is that known as atheroma or arteriosclerosis, which is especially common in the system of arterial trunks forming the circle of Willis. Fatty degeneration is often found in the vessel walls coincident with the increase in the connective-tissue elements. Calcification may occur and may be so extensive that the whole or a greater part of the circle of Willis is converted into a series of hard tubes usually somewhat larger than normal.[1] More commonly the calcareous areas are irregular in their distribution, giving to the vessels a

[1] *Marburg, O.*, Zur Pathologie der grossen Hirngefässe, Wien. klin. Wchnschr., 1902, xv, 1216; *Pick, A.*, Calcification of finer cerebral vessels, Amer. Jour. Insanity, 1905, lxi, 417; *Schmincke, A.*, Encephalitis interstitialis Virchow mit Gliose und Verkalkung, Ztschr. f. die ges. Neurol. u. Psychiat., 1920, lx, 290; *Bassoe, P.*, and *Hassin, G. B.*, Calcification of cerebral vessels, Arch. Neurol. and Psychiat., 1921, vi, 359.

nodular appearance. Fatty degeneration also occurs, though more rarely, as an independent lesion affecting the muscular coat. Hyaline degeneration may also occur either as an independent lesion, which is quite frequent in the brain of idiots, or as the initial lesion of a sclerosis.

The alterations in the brain substance associated with arteriosclerosis are usually the coarse hemorrhagic lesions of apoplexy; but in a certain number of brains with arteriosclerotic changes no gross lesions occur, and there are only minute focal areas of necrosis, most often in the gray substance of the cortex.[1] Limited secondary changes follow either the necrosis or the softening. These arteriosclerotic alterations in the brain are distinct from those due to paresis or senile dementia, both the latter involving the brain in a diffuse fashion and showing more or less characteristic structures.

DEGENERATION AND INFLAMMATION IN THE BRAIN, SPINAL CORD, AND NERVES.

Review of Normal Morphology.

While the scope of this work does not warrant a detailed description of the morphology of the nervous system,[2] our appreciation of the pathological changes to which it is subject is so dependent upon an accurate knowledge of its morphology, that, before proceeding further, a brief résumé of some of the more fundamental points in its structure and architecture cannot wisely be omitted.

The studies of Golgi and of his successors in the use of his technique have led to the so-called neurone conception of nervous-system structure. According to this view, the neurone represents the structural unit of the nervous system. The neurone is the nerve cell with all its prolongations, and the nervous system in toto is but an orderly association of an immense number of these neurone units. Although these neurones differ from one another as to details of structure they still present an essential similarity.

The neurone is first distinguishable as a small round cell in the epiblastic lining of the embryonic neural canal. Such a cell is entirely devoid of processes It soon, however, becomes pyriform, and from the tip of the pear grows out a process, which is the axis-cylinder process or axone. Later other processes appear as outgrowths of the cell body. These are the protoplasmic processes or dendrites. Each adult neurone then consists of a cell body, and passing off from this cell body two kinds of processes (Fig. 787 and 788).

The Cell Body.—Our knowledge of the internal structure of the nerve cell has been greatly increased in the last few years by the application of a special technique devised by Nissl.[3] Subjected to this technique, nerve cells present two very different types of reaction. Certain cells, such, for example, as the cells of the granule layers of the cerebellum and of the olfactory lobe, stain only as to their nuclei, the cell bodies themselves remaining entirely unstained. To such cells Nissl has given the name of *caryochromes*. It is obvious that the method of Nissl gives no insight into the structure of these cells. The majority of nerve cells, however, react both as to their nuclei and as to their cell bodies to the Nissl stain. These cells Nissl designates as *somatochromes*. Such a cell presents the following appearance (Plate XV, 1). There is a nucleus identical in structure with nuclei found in other cells. It is bounded by a nuclear

[1] *Marie*, Rev. de méd., 1901, xxi, 281.

[2] For this the reader is referred to *Barker, L. F.*, The Nervous System, New York, 1899; *Von Gehuchten, A.*, Anatomie du système nerveux de l'homme, 4th ed., Louvain, 1906; *Déjerine*, Anatomie des centres nerveux, Paris, 1895; *Edinger*, Bau der nerven. Zentralorgane, Leipzig, 1911; *Nissl* and *Alzheimer*, Histologische u. histopathologische Arbeiten, Jena, 1904–12; *Tilney, F.*, and *Riley, H. A.*, The Form and Functions of the Central Nervous System, New York, 1921.

[3] For Nissl's method see *Mallory* and *Wright*, Pathological Technique, 8th edition, p. 134.

membrane and traversed by a network which takes a comparatively light blue stain. Within the nucleus is a nucleolus staining an intense blue. In the cell body two distinct elements appear: a clear ground substance, unstained; and scattered through it deep staining masses, known as *chromophilic bodies*. These chromophilic bodies are granular, and differ in size, shape, and arrangement. These differences have served as a basis of classification. Presenting variations in different types of cells, their appearance in a given type remains constant. Most investigators, while differing in details, agree in ascribing to the unstainable substance a definite structure. This structure is usually described as composed of a fibrillar or reticular network lying in a more or less homogenous ground substance. With the use of the ordinary technique of Nissl, all of the cell body, excepting the chromophilic bodies, remains unstained and apparently structureless. Our ideas as to the physiology of these different elements of the nerve cell rest largely upon a theoretical basis. It has been shown that the nerve cell represents the genetic center of the neurone. From the behavior of the processes, when cut off from the nerve cell, it is evident that the cell body represents the nutritive or trophic center of the neurone. It seems probable that from the stand-point of neurone activity, the cell body represents the functional center of the neurone, while the processes act as organs of reception or distribution. Certain facts, such as the entire absence of the chromatic substance in many nerve cells, in the axones of all nerve cells, and its diminution during functional activity and in fatigue, together with its behavior under certain pathological conditions, lend weight to the view that the stainable substance of Nissl represents a food element of the cell. The achromatic element, on the other hand, is continuous with the fibrillæ of the axone, and is considered by most investigators as representing the essential nervous mechanism of the cell. The relation of the Nissl picture to the conditions existing in the protoplasm of the living cell still remains an unsolved problem. The importance of the Nissl method from the standpoint of pathology lies in the fact that when subjected to a given technique, a given type of nerve cell presents always the same appearance, and that this appearance furnishes a norm of comparison with cells showing pathological changes which have been subjected to the same technique.

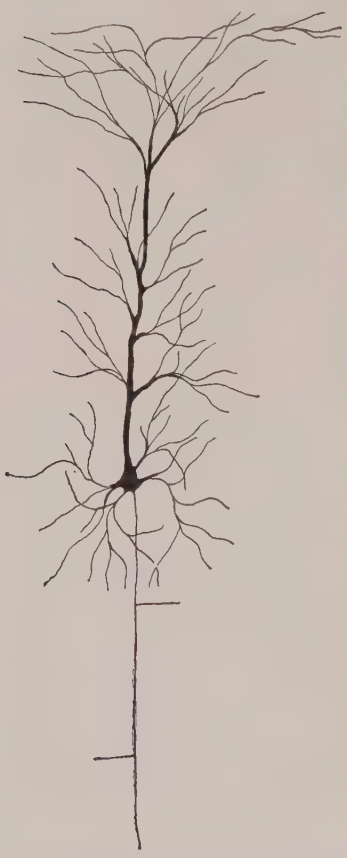


FIG. 787.—NEURONE (NERVE CELL OR GANGLION CELL AND PROCESSES) FROM HUMAN CEREBRAL CORTEX.

Showing main or apical dendrite passing upward and numerous smaller dendrites coming off from the main dendrite and from the body of the cell. A single axone (axis-cylinder process) passes downward from the base of the cell, giving off two collaterals.

Pigment.—In addition to the elements already described, more or less pigment in the shape of fine brownish yellow granules is often present in nerve cells (Plate XV). It is not found in cells of the new-born. It increases with age, and in old age often fills up a large part of the cell body. Its significance is not known.

The *protoplasmic processes* or *dendrites* are—at least the larger trunks—of the same structure as the cell body (Plate XV, 1). That these larger trunks have functions similar to those of the cell body seems probable from the fact that the axone not infrequently takes origin from a large dendritic trunk instead of directly from the body of the cell. The chromatic substance is present in the dendrites, as elongated

rods with triangular masses at the points of bifurcation. The achromatic elements are apparently of the same character as in the body of the cell. The protoplasmic processes divide dichotomously, becoming rapidly smaller, and end at a comparatively short distance from the cell body.[1] Stained by the method of Golgi, the dendrites are seen to be covered with minute projections or *gemmules*, often ending in a small bulb. These processes carry impulses toward the cell.

The *axis-cylinder process* or *axone*—so called from its often becoming the axis-cylinder of a nerve fiber—is usually single. It generally arises directly from the body of the cell, but may arise, as already mentioned, from one of the larger protoplasmic trunks. It is differentiated from the dendrites in Nissl preparations by always taking origin from an area in the cell body free from chromatic substance, the *axone hill*, and by being itself entirely achromatic (Plate XV, 1); in Golgi specimens, it is recognized by its straight course, uniform diameter, and smooth outline (Fig. 787). It sends off few branches, and these at right angles (collaterals.) This axone may extend a great distance from the cell body; for example, the axones of certain motor cells of the spinal cord extend to the muscles of the hands or feet. Both the axone proper and its collaterals end in terminal arborizations. Their conductivity is cellulifugal—that is, they always carry impulses from the cell. In certain cells the axis-cylinder processes branch rapidly and end in the gray matter in the vicinity of their cells of origin (Fig. 788). An axone may pass from its cell of origin to its termination uncovered by any sheath. Such axones are found in certain portions of the gray matter. An axone may be enveloped only by a thin membrane, the sheath of Schwann, as, e.g., the fibers of Remak found mainly in the sympathetic system. An axone may be surrounded by a myelin sheath alone, as in the white matter of the brain and cord, or by both a myelin sheath and a sheath of Schwann, as in the fibers of the peripheral nerves, with the exception of the olfactory and optic.

FIG. 788.—NEURONE (NERVE-CELL OR GANGLION-CELL PROCESSES). FROM THE GRANULAR LAYER OF THE CEREBELLAR CORTEX OF A GUINEA-PIG.

The short axone passes off to the left and terminates near its cell of origin.

According to the strict neurone conception of nervous-system structure, each neurone is considered a complete morphological and, to a lesser degree, physiological entity. It has no anatomical connection with any other neurone. Association between neurones takes place by contact or contiguity, and never by continuity of their protoplasm. The passage of an impulse is always from the terminal arborizations of axones or collaterals to the dendrites or cell body of the other neurone.

The validity of the neurone theory has been recently called in question by such prominent neurologists as Held, Apathy, Bethe, and Nissl,[2] on the ground that in many cases axones pass directly into the protoplasm of another neurone and that the neurofibrils are sometimes continuous throughout a series of neurones. Nissl in a critical review upon the present status of the neurone theory announces his belief that the entire neurone concept has been proved fallacious and must be abandoned.

Admitting that the discovery of anastomoses between neurones and of the continuity of the neurofibrils must be accepted as invalidating some of our ideas as to the separateness of the neurone units, it can still hardly be considered as overthrowing the entire neurone theory. Embryologically, morphologically, and physiologically the neurone shows a marked degree of individuality, and the fact that neurones sometimes, usually, or even always, anastomose no more warrants the giving up of the neurone as essentially a unit than did the discovery of the fact

[1] Exception, peripheral arm of spinal ganglion cell.

[2] For a critical view of the opinions of these writers consult *Van Gehuchten, A.*, Anatomie du système nerveux de l'homme, 4th ed., Louvain, 1906.

Explanation of Plate XV.[1]

1. Normal Ganglion Cell. Large motor cell from anterior horn of human spinal cord, showing the nucleus in its normal central position with its nucleolus. In the body of the cell are seen the chromophilic bodies of various shapes and sizes. Three main protoplasmic trunks or dendrites pass off from the upper portion of the cell. In these the chromophilic bodies are rod-shaped. The largest process branches at a short distance from the cell. To the left is seen the axone or axis-cylinder process free from chromatic substance, as is also that portion of the cell from which it takes origin (axone hill).
2. Ganglion Cell from the Anterior Horn of the Human Spinal Cord of a Case of Alcoholic Neuritis. Showing eccentricity of the nucleus and a large central area of the cell body free from chromatic substance (central chromatolysis), with an arrangement of the remaining chromophilic bodies around the periphery. (The similarity between the appearance of this cell and the one shown in Fig. 6 should be noted.)
3. Ganglion Cell from the Anterior Horn of the Spinal Cord of a Rabbit Inoculated with Rabic Virus and Killed Shortly After the Onset of Symptoms. Shows an early stage of chromatolysis; the chromophilic bodies being pale, ragged, and vacuolated.
4. Ganglion Cell from the Anterior Horn of the Spinal Cord of a Rabbit which Died on the Ninth Day After Inoculation with Rabic Virus. Shows extreme chromatolysis, only a few fine granules of chromatic substance remaining at the periphery. The cell is swollen, the nucleus has disappeared, and the cell body and processes are stained more deeply with the erythrosin than is the case in normal cells.
5. Normal Ganglion Cell from a Human Spinal Ganglion of the Posterior Root. Showing central position of the nucleus and the concentric arrangement of the chromophilic bodies.
6. Ganglion Cell from the Posterior Root Ganglion of a Rabbit Three Weeks After Section of the Sciatic Nerve. The cell shows extreme eccentricity of the nucleus with central chromatolysis and a peripheral arrangement of the remaining chromophilic bodies—axonal degeneration. (There also remains in the central portion of the cell some chromatic substance in the shape of fine granules forming an irregular reticulum. The similarity between this picture and the one shown in Fig. 2 is apparent.)
7. Portion of a Posterior Root Ganglion from a Case of Tabes Dorsalis. Showing degeneration in the ganglion cells with increase in the interstitial connective tissue.
8. Two Pyramidal Cells from the Normal Human Cerebral Cortex. While the pyramidal cells in the human cortex vary considerably in the amount of chromatic substance which they contain, these are of an average type.
9. Two Pyramidal Cells of the Human Cerebral Cortex from a Case of Eclampsia. These cells show marked chromatolysis.
10-13. Anterior Horn Cells of the Spinal Cord from a Case of Pellagra. Showing coarse Nissl granules (Fig. 10), clumping of the granules and disappearance of the nuclear boundaries (Fig. 11), pigmentation with absence of nuclei (Fig. 12), and absence of nucleus and breaking up of Nissl granules (Fig. 13).

[1] In the staining of the specimens from which these drawings were made, Held's modification of Nissl's method was used. This consists essentially in a preliminary staining of the sections with a one per cent. aqueous solution of erythrosin. In the case of the specimens used for the last four drawings (Fig. 10–13), the regular Nissl staining method without the erythrosin counterstain was employed.

FIG 1

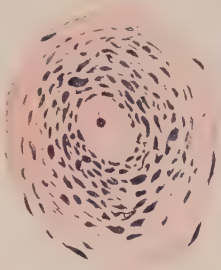


FIG 5

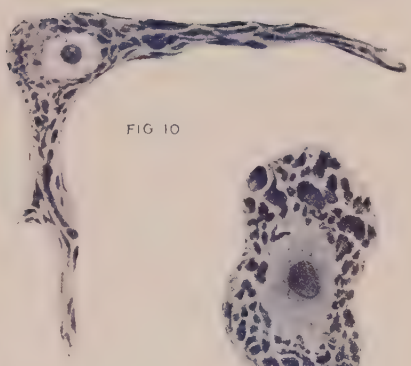


FIG 10

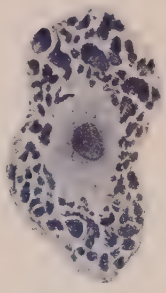


FIG 11

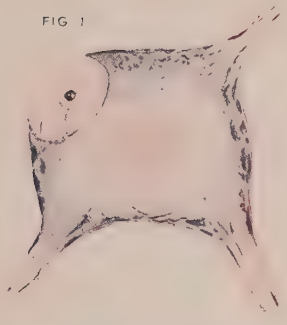


FIG. 2.

FIG 6

FIG 12

FIG. 3.

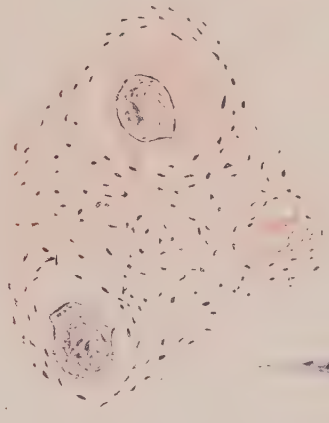


FIG 7

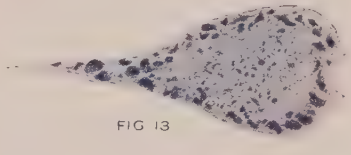


FIG 13

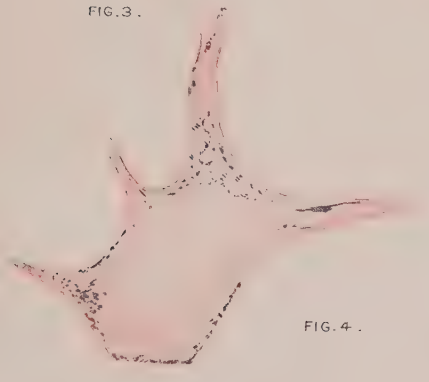


FIG. 4.

FIG 8

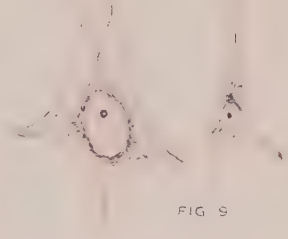


FIG 9

Lesions of Ganglion Cells.—(Stained by Nissl's Method)

SACKETT & WILHELMS CORP. N. Y.

that the protoplasm of epithelial cells was continuous through intercellular "bridges" necessitate the giving up of the epithelial cell as the structural unit of epithelium.

The cell bodies of neurones are grouped mainly in the gray matter of the brain and cord, in the ganglia of cranial, spinal, and sympathetic nerves, and in the peripheral end organs of certain of the nerves of special sense. Protoplasmic processes ramify mainly within the gray matter.[1] While some terminate in the gray matter in the immediate vicinity of their cells of origin, it is the axones that make up the bulk of the white matter of the brain, cord, and peripheral nerves.

Neuroglia.—In addition to the extensions inward of the pia mater and the connective tissue of the blood-vessels, there is found in both gray and white matter a tissue, supportive and protective in function, and peculiar to the nervous system—the neuroglia. Like the neurone, it originates in the epiblastic cells lining the embryonic neural canal. These cells, at first morphologically identical, soon differentiate into neuroblasts or future neurones, and spongioblasts, or future neuroglia cells. In the adult two main types of neuroglia cells are found, spider cells (Fig. 789), with spine-like, straight, unbranching processes, and mossy cells (Fig. 790) with thick, rough, branching arms. The former are found chiefly in the white matter, the latter in the gray matter in connection with blood-vessels. As in the case of the nerve cell, the processes of these cells do not anastomose, but interlace, forming a dense feltwork. By a special stain, Weigert demonstrates neuroglia cell nuclei and separate fibrils. It seems probable that this method fails to show the body of the cell, while staining its nuclei and the fibrils which pass through it.

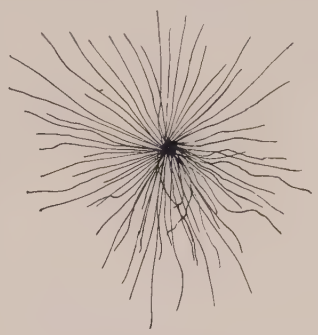


Fig. 789.—Neuroglia Cell—Spider Type—Human Cerebrum.

It would thus appear that the architecture of the central nervous system, considered as an organ, is analogous to that of other organs. It has in the neurone its parenchyma, and this parenchyma is supported and bound together by a framework of connective tissue. The essential difference lies in the fact that in the neurone is the highest morphological differentiation which protoplasm has attained, representing chemically the most complex molecules known. In the axone, sometimes a meter or more in length, of a cell of microscopic dimensions, there is a distribution of cell protoplasm, such as occurs in no other tissue or organ. The neuroglia also, while without question a tissue supportive in function, is embryologically and morphologically different from other forms of connective tissue.[2]

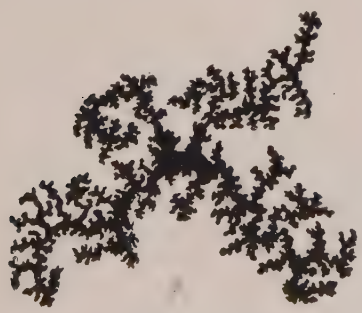


Fig. 790.—Neuroglia Cell—Mossy Type—Human Cerebrum.

DEGENERATION.

Neurone Degeneration.

Degenerative changes may affect the entire neurone or any of its parts. Such changes may result from direct injury to some part of the neurone, to diminution or modification of its nutritive supply, to various toxic conditions, etc.

I. Changes in the Neurone from Injury to One of Its Parts.—(*a*) Changes in the Axone Resulting from Separation from Its Cell Body.—That changes, presumably of a

[1] Exception, peripheral arm of spinal ganglion cell.

[2] For detailed investigation of neuroglia, see *Weigert, C.*, Gesammelte Abhandlungen, Berlin, 1906, ii, 582; and *Alzheimer, A.*, Nissl and Alzheimer, Histologische und histopathologische Arbeiten, Jena, 1910, iii, 401.

degenerative character, occur in the peripheral end of a nerve when its connection with the central nervous system is broken has long been known. This degeneration takes place as well in the central as in the peripheral nervous system, and is complete, involving every portion of the axone distal to the point of section. The changes are not progressive from the point of lesion, but occur at nearly the same time in all parts of the distal stump. These changes consist in a breaking up of the medullary sheath into segments (Fig. 791), which in turn disintegrate, forming variously shaped masses of myelin, among which may be seen the axis-cylinder, the whole being inclosed by the neurilemma. The osmic acid method of Marchi, which differentiates between fat and myelin, shows that coincident with the breaking up of the myelin there is an appearance of fat droplets. These fat droplets increase in number *pari passu* with the decrease in myelin, but also ultimately disappear. During the progress of these changes in the medullary sheath, the axis-cylinder at first segments and then undergoes dissolution. The neurilemma, on the other hand, appears to take no part in the degenerative process. On the contrary, it and its nuclei remain intact to take part later in regenerative changes, should these occur. If there is no reunion of the severed ends of the axone, the peripheral portion completely disappears, its place being taken by connective tissue.

FIG. 791.—NEURONE DEGENERATION AFTER INJURY.

Teased nerve fibers from distal portion of sciatic nerve of rabbit three weeks after division of the nerve. Osmic-acid stain. The large and small black masses represent disintegrated myelin and fat droplets.

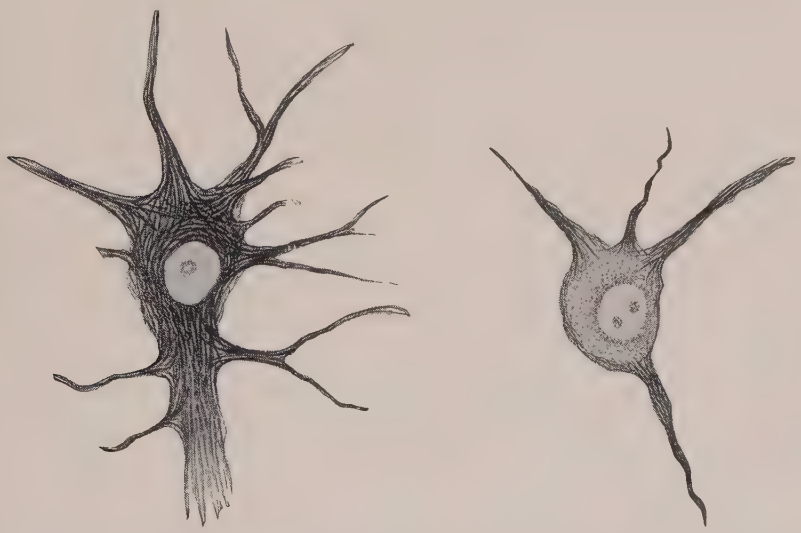
(*b*) CHANGES IN DENDRITES RESULTING FROM THEIR SEPARATION FROM THEIR CELL BODIES.—If we consider, as some observers do,[1] that the peripheral arm of the spinal ganglion cell is a protoplasmic process, making a physiological rather than a morphological differentiation, we find that the same law holds good for dendrites as for axones when separated from their cell bodies. Thus in the divided peripheral nerve those fibers which are the processes of the spinal ganglion cells undergo the same degenerative changes as do the fibers which are processes of cells of the anterior horn. Most dendritic processes are, however, so short and terminate in the gray matter so near the cells from which they originate that experimental separation of the process from its cell body is impracticable. In view of the fate of the axone, however, and the relation of the dendrites to the cell body, there can be little doubt that as complete degeneration follows the severance of a protoplasmic process from its cell of origin as follows in the case of the axone.

(*c*) CHANGES IN THE PROXIMAL STUMP AND IN THE CELL BODY RESULTING FROM LESION TO THE AXONE.—The fundamental principle of the law of Waller was the complete degeneration of the distal portion of the divided nerve, while the proximal stump remained intact. Our present conceptions, however, of the interdependence of the different

[1] *Van Gehuchten, A.*, Anatomie du système nerveux de l'homme, 4th ed., Louvain, 1906.

parts of the neurone, and of the axone as the outlet for neurone energy, would lead us to expect certain changes of an atrophic nature in the proximal stump and in the cell body, as a result of separation from its axone and consequent inability to functionate. That such changes take place recent improvements in cytological technique have enabled us to determine. The method of Marchi shows that degenerative changes occur, not only in the distal, but in the proximal end of the divided nerve. These changes take place more slowly than in the distal portion, but are apparently identical in character.

In the body of the cell the method of Nissl demonstrates marked changes after section of the axone. These changes may be observed



A *B*

FIG. 792.—*A*, Fibrils in normal anterior horn cell. *B*, Fibrils in degenerated cell after separation from its motor nerve. After Bielschowsky. Bielschowsky fibril stain.

within twenty-four hours after the injury. They consist in a diminution in the chromatic elements of the cell, chromatolysis. This is most marked in the central portion (central chromatolysis), a distinct ring of chromophilic bodies around the periphery often remaining. The nucleus usually migrates toward the periphery and may even bulge from the cell. The fibrils in the cell body also show changes (Fig. 792, *A* and *B*). In the case of the hypoglossal nerve in the rabbit, these changes reach their maximum in from two to three weeks. The future of some of these cells is complete degeneration. Others apparently undergo hypertrophy and regeneration. The fibrils, as demonstrated by the silver impregnation methods, decrease in number and stain only at the periphery of the cell and in the dendrites. The cell may not regenerate after this phase. If regeneration does take place, however, the cell may enlarge and the fibers reappear; but ultimately the cell may again

degenerate and the fibers disappear.[1] The intensity of the reaction of the nerve cell to injury to its axone depends upon the severity of the injury. Thus cutting the nerve is followed by more prompt and marked changes in the nerve cell than simple compression, while pulling out the nerve roots is followed by a still more intense reaction. Again, there is a difference in the resisting-powers of different types of cells. Thus the motor cells of the anterior horn are peculiarly resistant to injury to their axones, as are also the spinal ganglion cells to injury to their central processes. Again, between cells of the same type there are marked variations in resisting-powers. Thus the motor cells of the anterior horn are much more resistant than the cells of the motor cranial nuclei.[2]

(*d*) Changes in the Cell Body Resulting from Lesions to Its Dendrites.—In the study of the effect upon the cell body of a lesion depriving it of one or all of its dendritic processes, we meet with the same experimental obstacles already mentioned in connection with changes in the dendrites. It is, again, only in the peripheral arm of the spinal ganglion cell that we have a cellulipetal process of any considerable length. Section of this process results in changes in the spinal ganglion cell quite similar in character to the so-called "axonal" degeneration (Plate XV, 6). If we consider that a cell's dendrites probably furnish its most important avenue for the reception of impulses, it follows that a neurone may be thrown as completely out of circuit, as it were, by injury to its dendrites as by injury to its axons. Interesting experiments[3] have been carried out in the attempt to bring about the same functional effect as would result from section of a cell's dendrites, by inhibiting afferent impulses. Cutting the posterior roots resulted in changes in the cells of the anterior horn. The inference was that these changes were induced by an inhibition of the customary normal stimulation by means of the afferent impulses reaching the cells through their dendritic processes.

II. Changes in the Neurone from Interference With Its Nutrition.—Changes apparently of a degenerative character have been described in neurones as a result of interference with nutrition Thus it has been[4] found that by temporarily applying a ligature to the abdominal aorta, an acute necrosis of the cells of the lumbar cord can be induced. Later experiments of a similar nature followed by the Marchi staining showed that the degenerative process affected not ony the cell bodies, but the entire neurone. Similar degenerative changes have been induced by experimentally produced multiple emboli, cells in the vicinity of the occluded vessels being in marked contrast to cells from regions whose vessels remained patent. Definite degenerative changes have been seen[5]

[1] For studies of regeneration of peripheral nerve fibers, see *Kennedy*, Brit. Med. Jour., 1904, ii, 729; *Head* and *Ham*, Jour. Physiol., 1904–05, xxxii, 9; and *Doinikow, B.*, Nissl and Alzheimer, Histologische und Histopathologische Arbeiten, Jena, 1911, iv, 445.

[2] For review and bibl. of changes in the nerve cell and in the proximal stump after section of a peripheral nerve, consult *Barker, L. F.*, The Nervous System, New York, 1899; and *da Fano*, Zieglers Beitr., 1908, xliv, 495.

[3] See *Warrington, W. B.*, Jour. Physiol., 1898, xxiii, 112, for study of the structural alterations in nerve cells.

[4] See *Brieger* and *Ehrlich*, Ztschr. f. klin. Med., 1884, vii, Suppl., 155.

[5] For study of ganglion cells, see *Ewing, J.*, Arch. Neurol. and Psycho-Path., 1898, i, 263.

in nerve cells as a result of anemia consecutive to pressure from cerebral hemorrhage and to thrombosis of the basilar artery. Less marked changes have been observed in cases of general malnutrition and in severe anemias, except the pernicious form, in which extensive cerebral and spinal lesions, due perhaps to a special toxin, may occur.[1]

III. Effects of Toxins upon Neurones.[2]—Changes of a degenerative character occur in neurones as a result of the action of toxins. These toxins may be introduced into the body from without, for example, such poisons as alcohol, arsenic, lead, strychnin, etc.; they may be elaborated within the body as the result of faulty metabolism, for example, in uremia, eclampsia, etc., or as a result of the action of bacteria, as in tetanus, rabies (Plate XV, 3, 4, and 8), diphtheria, etc., or of the Plasmodium malariæ. The effects of these poisons upon the neurone vary with different poisons and in different types of neurones. The effects of the same poison upon a given type of neurone also vary according to its rapidity of action, whether rapidly fatal or extending over a considerable period of time. Again, given the same poison and the same time of action, not all neurones even of the same type show an equal susceptibility.

These changes in the neurone from the action of toxins may affect one or all of its structural elements, and vary from the slightest appreciable loss of staining qualities of the chromophilic bodies to complete destruction of the neurone. In the chromophilic bodies the essential change seems to be a decrease in the amount of chromatic substance, *chromatolysis*. This may be evidenced merely by a decreased staining intensity, the chromatic masses appearing abnormally pale; the bodies may have a ragged or frayed-out appearance at their edges; they may be shrunken, or, retaining their normal shape and size, become vacuolated (Plate XV, 3); they may completely disintegrate, giving to the cell a diffuse granular appearance; they may disappear, leaving the cell entirely devoid of chromatic substance. The chromatic masses in the dendrites seem in many cases to be more resistant or less exposed than are those in the body of the cell, often remaining unchanged at a time when the latter show an advanced degree of chromatolysis. During these changes in the chromatic element the cyto-reticulum may remain apparently normal or it may more or less completely disintegrate. This disintegration usually marks the more advanced degenerative changes (Plate XV, 4).

In the truly achromatic element of the cell or cytoplasm, our present methods of staining fail to demonstrate lesions except in the finer fibrillar structures. Diffuse staining of this basement substance is a common phenomenon of chromatolysis, but seems more properly referable to a diffusion of the fine granules resulting from disintegration of the chromatic masses than to any changes in the cytoplasm itself. Disappearance of the formed elements of the cell often leaves clear holes or vacuoles in the cell body or gives the appearance of cracks or fissures. The nucleus may remain normal; it may swell and its contour become abnor-

[1] *Wolman, H. W.*, Arch. Int. Med., 1918, xxi, 791 (bibl.).

[2] *Meyer, A.*, On parenchymatous systemic degenerations mainly in the central nervous system Brain, 1901, xxiv, 47.

mally distinct; it often takes a diffuse stain; later it shrinks, becomes crenated, its reticulum and limiting membrane break up and its outline is lost. During these nuclear changes the nucleolus may also disintegrate, but it is often extremely resistant, remaining apparently unchanged after most of the other parts of the cell have become unrecognizable. Concurrent with these changes in internal structure are changes in the shape and size of the cell. Its contour becomes irregular, and its edges present an eroded appearance; the cell body shrinks away from its cell space, breaks up, and ultimately disappears. The dendrites undergo alterations similar to those in the body of the cell. They shrink, become separated from the cell body, and finally disintegrate.

That part of the neurone which shows most marked evidences of its effect is not necessarily the part upon which the poison is most directly acting. Thus a toxin affecting directly the cell body may cause the earliest and most pronounced changes far out in its dendritic or axonal processes, that is, in those parts of the neurone farthest removed from the trophic center.

To the action of a specific poison certain neurones seem less resistant than others. Thus, to the action of lead those neurones governing the extensor muscles of the wrist seem especially susceptible. The cells of the motor nucleus of the trigeminus seem to be less resistant than other motor cells to the poison of tetanus. Again, the frequency with which tabes dorsalis is associated with a syphilitic history seems to indicate a special susceptibility to the syphilitic poison on the part of the peripheral sensory neurone.

Comparing the changes in the nerve cell in toxemias (Plate XV, 3 and 4) with those induced by lesions to its axone—axonal degeneration (Plate XV, 6)—we note that while in the latter the chromatolysis is central in character, beginning in the region of the axone hill and nucleus, in the former the changes begin at the periphery, the portion of the cell in most direct relation to the surrounding lymph. In axonal degeneration the nucleus is usually eccentric. In toxemia it usually remains central, at least until the process of degeneration is far advanced. While this distinction holds good in general and while the phenomena of central chromatolysis and eccentricity of the nucleus regularly follow injury to the axone, we are not yet warranted in stating that such changes never occur except after some injury, or that the presence of such changes in the cell can be explained only on the basis of injury to its axis-cylinder.

IV. Effects of Fatigue upon Neurones.—Studies of the effect of fatigue upon the neurone have been made in animals after prolonged muscular activity and after electrical stimulation. Changes have been described which consist in a decrease in the size of the cell body, a decrease in the size of the nucleus, often with distortion, and a marked increase or decrease in the amount of chromatic substance with more or less diffuse staining of both cell body and nucleus.[1] There is no agreement as to the direct relationship of these changes to fatigue, and many observers deny that such morphological alterations are constant in this condition.[2] Changes consist in a decrease in the size of the cell body,

[1] *Hodge*, Jour. Morphol., 1892, vii, 1; *Dolley, D. H.*, Jour. Med. Research, 1909, N. S. xvi, 95; and Jour. Am. Med. Assn., 1917, lxviii, 756; *Crile, G. W.*, A Physical Interpretation of Shock, Exhaustion, and Restoration, New York, 1921.

[2] *Kocher, R. A.*, Jour. Am. Med. Assn., 1916, lxvii, 278.

a decrease in the size of the nucleus, often with distortion, and a marked increase or decrease in the amount of chromatic substance with more or less diffuse staining of both cell body and nucleus.

It seems not at all improbable that the clinical pictures presented by certain psychoses and neuroses are the expression of the effects upon the neurones of prolonged fatigue. Certain local expressions of neurone exhaustion, as, for example, writer's cramp, may possibly also be placed in the same category.

As to the significance of those changes in the nerve cell, which are marked by diminution in the chromatic substance alone, and to which the term "chromatolysis" has been given, there is a considerable difference of opinion. Marinescu considers them of the nature of degeneration, while Van Gehuchten[1] is inclined to look upon the phenomenon as conservative in character, a means by which the neurone assumes a condition most advantageous for self-defence. It has been shown that even an extreme degree of chromatolysis is not incompatible with function. Marinescu insists that so long as the changes are confined to the chromatic substance recovery is possible, no matter how extensive the alterations, while changes in the achromatic elements are always permanent in character.

REGENERATION.

Regeneration of nerve tissue in the sense of an actual reproduction of neurones probably never occurs in the adult human nervous system.[2] As has been noted, extreme chromatolysis may be succeeded by complete recovery. In the case of axonal chromatolysis, the degenerative process usually reaches its maximum in about three weeks. Regeneration of chromophilic bodies then begins. This reconstructive process is slow, the cells often requiring months to return to a normal condition. At some stage of the process there is usually an overproduction of chromatic substance, and the cells appear darker than normal.

Primary union between the ends of divided nerve fibers does not occur. Complete degeneration of the distal portion always precedes the regenerative process. In this reconstruction the nuclei of the neurilemma seem to play an important part; they increase in number, and there is also an increase in the protoplasm which surrounds them. With union of the divided ends, the axones of the central stump may grow out again, if the ganglion cells be intact, and ultimately resume function. The myelin first reappears as droplets which coalesce and finally form a complete sheath. This reconstructive process in the nerve fiber is extremely slow, often requiring many months for its completion.[3]

Replacement Neuroglia Hyperplasia.[4]—Under various conditions in which there is destruction of the parenchyma, as, for example, in ascending and descending degenerations of the spinal cord, there occurs a compensatory increase in the interstitial elements. This new tissue is at first cellular, most of the cells being of the spider variety. Later there

[1] See *Van Gehuchten, A.*, Anatomie du système nerveux de l'homme, 4th ed., Louvain, 1906.

[2] For review and literature on regeneration, see *Barker, L. F.*, The Nervous System, New York, 1899, p. 245 and following.

[3] For studies of the regeneration of peripheral nerve fibers, see *Kennedy*, Brit. Med. Jour., 1904, ii, 729; *Head* and *Ham*, Jour. Physiol., 1904–05, xxxii, 9; and *Doinikow, B.*, Nissl and Alzheimer, Histologische und histopathologische Arbeiten, Jena, 1911, iv, 445; and *Huber, G. C.*, Transplantation of peripheral nerves, Arch. Neurol. and Psychiat., 1919, ii, 466; 1920, iii, 437.

[4] *Alzheimer, A.*, Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen den Abbauvorgangen in Nervengewebe, Nissl und Alzheimer, Histologische und histopathologische Arbeiten, Jena, 1910, iii.

is an increase in the neuroglia fibers, and the tissue often becomes dense and hard. What part the mossy cells or other less common types of neuroglia cells take in the proliferative process is as yet unknown. With the increase in fibers there are often shrinkage and the formation of dense fibrous tissue. This replacement hyperplasia in neuroglia seems quite similar in nature to replacement connective-tissue hyperplasia in other organs, and is often wrongly considered inflammatory.

Degenerations Affecting Systems of Neurones.

General Considerations Concerning Neurone Systems.

Before considering the subject of systemic degeneration we may refer briefly to the situation in the nervous system of certain of the more important groups of neurones and the paths which their axones take.

That the cell bodies of neurones are grouped in the gray matter of the brain, cord, and ganglia, and in the end organs of certain nerves of special sense, has already been mentioned. This grouping of neurones serves definite physiological ends. Their cell bodies form centers or nuclei, while their axones are collected into bundles or fiber tracts. Thus, in the region of the fissure of Rolando are grouped the centers of those neurones which have to do with voluntary motion, and what is known as cerebral localization means the grouping of cell bodies of neurones for specific function. After the known localizations are eliminated, there still remains unaccounted for the greater part of the cerebral cortex, and our present belief is that these neurones are neurones of association by which the various centers are brought into physiological relationship. Some understanding of this neurone grouping, and especially of the arrangement of their neuraxones as fiber tracts of the cord, is essential to an appreciation of those degenerations which affect definite systems of neurones.

Peripheral Motor Neurones.—These neurones have their cell bodies in the gray matter of the anterior horn and in the motor nuclei of the cranial nerves. Their neuraxones pass out as the motor fibers of the cranial and of the spinal nerves. The entire neurone lies upon the same side of the body; that is, the peripheral motor neurone is "direct."

The Upper or Corticospinal Motor Neurones have their cell bodies situated mainly in the cerebral cortex near the fissure of Rolando. Their neuraxones converging, pass through the internal capsule, pons, and medulla, sending off fibers to the motor nuclei of the cranial nerves. In the medulla the tract comes to the surface as the *anterior pyramids*. At the junction of medulla and cord occurs the pyramidal decussation in which most of the fibers of the tract cross to the opposite lateral region of the cord, to be known as the *crossed pyramidal tract*, while a minority remain on the same side, to pass down the cord as the *direct pyramidal tract*. As the tracts descend, fibers continuously leave them to terminate, those of the crossed tract in the gray matter of the same side, those of the direct tract, after passing through the anterior commissure, in the gray matter of the opposite side. The corticospinal motor tract is a crossed tract.[1] These tracts present variations in size and length. They are often asymmetrical. The crossed tract extends to the lower sacral cord. The direct tract usually ends about the mid-dorsal region, though it has been followed as low as the second lumbar segment.

The Sensory (Afferent) Tract, like the motor, consists of two segments, an upper and a lower.

The lower or peripheral sensory neurone tract has its cell bodies in the ganglia of the spinal and of the cranial nerves. Their peripheral arms, which Van Gehuchten considers protoplasmic processes, are axis-cylinders of cranial or of spinal nerves. Their central processes or axones pass into the cord as the fibers of the posterior roots and enter the posterior columns. Here they divide into ascending and descending arms.

[1] Certain recent observations tend to show that there may be a small number of "direct" fibers in the so-called crossed pyramidal tract.

The descending arm is short, and with its collateral branches soon terminates in the gray matter of the same side of the cord. The ascending arm may also be short, and with its collaterals terminates as does the descending. It may pass a considerable distance up the cord and then end in the gray matter. It may, as one of the long fibers of the posterior columns, continue upward to the medulla, where it terminates in one of the posterior column nuclei. These long fibers pass inward as they pass upward, so that the lower the origin of the fiber the more mesial is its position in the upper part of the cord. The entire neurone lies upon the same side of the cord. The lower sensory, like the lower motor neurone, is direct.

Upper Sensory Neurones.—The arrangement of these neurones is extremely complex, and only those whose axones enter into the formation of distinct tracts of the cord will be here mentioned. Of the above-described central arms of the peripheral sensory neurones, some of the shorter enter the gray matter of the cord and with their collaterals terminate around motor cells (reflexes). Others terminate around cells whose axones cross to the opposite side of the cord and pass upward as the anterolateral ascending tract, or tract of Gowers. Other fibers terminate around cells of the column of Clarke, the axones of which pass upward as the direct cerebellar tract.

In addition to these main fiber tracts, there are in all regions of the cord fibers which are commissural in character. These fibers are the axones of cells situated in the gray matter of the cord, and after passing a short distance up or down and sending collaterals into the gray matter, themselves re-enter the gray matter and terminate there. These short fibers make up the so-called ground bundles or fundamental columns of the cord. They attain their greatest development in those regions of the cord where the reflex centers are most extensive, that is, in the lumbar and cervical enlargements.

Secondary Degenerations.

Secondary degenerations are dependent upon the fact already noted, that, the cell body being the trophic center of the neurone, the axone when separated from its cell body dies.

Descending Degeneration.—Any cortical lesion, such as embolic softening and apoplectic clots, which destroys the nerve cells, or any lesion of the brain or cord which interrupts the axone tracts of the corticospinal system of neurones, determines a complete degeneration of the affected axones (Fig. 793). The course of these axones has been described. Thus a lesion of the brain affecting motor neurones is followed by a degeneration in the motor tract of the same side down to the pyramidal decussation, and below that point, in the direct motor tract on the same side and in the crossed tract on the opposite side, the number of degenerated fibers being proportionate to the number of cells destroyed or axones interrupted. In a number of cases of descending degeneration due to cerebral lesions, degenerated fibers were found in the crossed pyramidal tract on the same side as the lesion. This degeneration was not present in all cases, and in no case was it so marked as the degeneration in the opposite lateral tract. The explanation is that in some cords a small number of fibers instead of decussating pass down into the cord in the lateral tract of the same side.

In descending degeneration due to a lesion below the pyramidal decussation a somewhat different picture is presented. In a complete transverse lesion there is degeneration of both crossed and of both direct pyramidal tracts. If the lesion is unilateral the degenerations are upon the same side as the lesion. The areas of degeneration are also larger and

less sharply defined than in cerebral lesions. Then in addition to the degeneration of the pyramidal tracts there is a degeneration of a con-

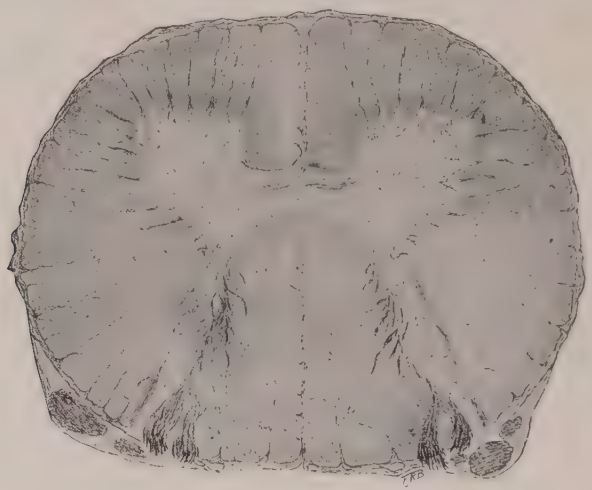


FIG. 793.—SECONDARY DESCENDING DEGENERATION.

From hemorrhage into the internal capsule, almost complete degeneration of the direct pyramidal tract on the same side as the lesion and of the crossed pyramidal tract on the opposite side. There were a few degenerated fibers in the crossed tract on the same side as the lesion.

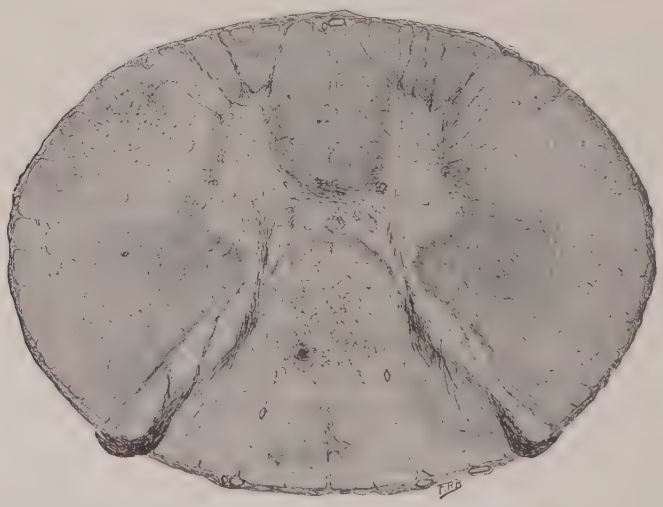


FIG. 794.—SECONDARY ASCENDING DEGENERATION.

Following complete crushing of the cord about two segments below the level at which the section was taken. Degeneration is almost complete in the columns of Goll, of Gowers, and the direct cerebellar tracts. A few normal fibers are seen in the columns of Burdach. These are the ascending axones of spinal ganglion cells between the point of injury and the level of the section, and are seen to occupy that part of the posterior columns adjacent to the posterior horns.

siderable number of fibers in a crescent-shaped area lying near the periphery of the anterolateral region and extending from the crossed to the direct tract. Degeneration of these fibers has been described[1] after

[1] *Marchi*, Riv. sper. di freniat., 1891, xvii, 367.

removal of the cerebellum. They have been considered as descending cerebellar fibers. The so-called comma-shape degeneration in the posterior columns is sometimes present. Others[1] regard these fibers, which are situated about the middle of the posterior columns, as descending axones of spinal ganglion cells, while still others[2] think that they are more probably descending branches of commissural neurones. In the fundamental columns the degeneration extends but a short distance below the seat of injury, and of course affects only descending axones.

Ascending Degeneration.—Any lesion which destroys the spinal ganglion cells or which interrupts their axones determines a secondary ascending degeneration in the posterior columns (Fig. 794). Any lesion of the cord which interrupts the tract of Gowers or the direct cerebellar tract is followed by degeneration of the fibers of these tracts above the lesion (Fig. 794). Immediately above the lesion there is complete degeneration of the tracts. As we pass upward new undegenerated fibers from the spinal ganglia above the lesion enter the column of Burdach, so that there appears in the posterior columns a constantly increasing number of normal fibers. Also in the column of Gowers undegenerated fibers appear as one passes upward from the lesion. Some of these fibers probably have their origin in the gray matter of the cord, and the number of normal fibers is in proportion to the number of these cells between the lesion and the point at which the section is taken. Descending fibers in these columns have already been mentioned. They, of course, do not degenerate. If the lesion be above Clarke's columns the degeneration in the cerebellar tracts remains complete; if not, the number of normal fibers is in proportion to the number of Clarke's column cells between the lesion and the point of section. The ascending fibers of the fundamental columns also degenerate, but are so short that they cannot usually be traced beyond the area of direct action of the traumatism.

Primary Degenerations.

Degeneration of the Peripheral Motor Neurones.

Progressive spinal muscular atrophy is the clinical designation of a disease, the underlying lesion of which is a progressive atrophy or degeneration of the lower motor neurones. There is a degeneration of the large motor cells of the anterior horns and of their processes.[3] This degeneration goes on to complete destruction of some neurones. With the loss of nerve tissue proper there is a compensatory growth of neuroglia. In a well-advanced case, section of the cord shows a marked diminution in the number of anterior horn cells and an atrophic condition of the horn itself and of the anterior roots. The lesion usually begins in the cervical region; more rarely it starts in the lumbar cord. The degeneration may extend to the motor cranial nerve nuclei, giving the

[1] *Schultze*, On Comma-shaped Degeneration of the Posterior Columns, Arch. f. Psychiat., 1889, xi, 770.

[2] *Tooth, H. H.*, Gulstonian Lectures on Secondary Degenerations of the Spinal Cord, London, 1889.

[3] *Huenekens, E. J.*, and *Bell, E. T.*, Infantile spinal progressive muscular atrophy (Werdnig-Hoffmann), Amer. Jour. Dis. Chil., 1920, xx, 496.

picture of a progressive bulbar paralysis. The medullary nuclei most commonly involved are the hypoglossal and the spinal accessory. Less often the degeneration affects the cells of origin of the fifth and seventh. Degeneration of the peripheral nerves has been described. The muscular lesions correspond to the lesions in the cord, the muscles of the hand and arm being usually first affected. The affected muscles are pale and infiltrated with fat. The fibers shrink, and the contents of the sarcolemma sheath become granular and finally disappear, leaving nothing but the sheath and the nuclei. This lesion is sometimes described as a chronic anterior poliomyelitis. Both its clinical history and its pathology, however, indicate the degeneration as the initial lesion and the neuroglia increase as secondary—a replacement hyperplasia. The vascular lesions which have been found also point to a primary degenerative change. The disease is probably syphilitic in origin in about one-fifth of the cases; heavy muscular labor and hereditary weakness of the affected neurones are unquestioned factors, also.

Degeneration of the Corticospinal Motor Neurones.

Spastic Paraplegia—Spastic Spinal Paralysis.—This may be described as a primary lesion of the upper or corticospinal motor neurones. Arteriosclerosis and syphilis may be etiological factors.[1] It is probable that the lesion affects the entire neurone. As a distinct pathological entity the condition is extremely rare. Whether it originates in a degeneration of the cell bodies of these neurones in the cortex is not known. The lateral columns and especially the pyramidal tracts are degenerated, and there is a replacement gliosis. The clinical picture of spastic paraplegia due to compression, to a transverse myelitis, or to a multiple sclerosis, is not uncommon. The type of spastic paraplegia appearing in childhood is due to a faulty development of the corticospinal motor neurones, rather than to their degeneration (*Little's disease*).[2] Probably some cases are due to porencephalus, polioencephalitis, or birth injuries inhibiting the development of the pyramidal tracts.

Degeneration of Both Peripheral and Corticospinal Motor Neurones.

Amyotrophic Lateral Sclerosis.—This is a primary progressive degeneration involving both corticospinal and spinoperipheral motor neurones. The appearance of the transverse section of the cord is a combination of that in spastic paraplegia and that in progressive muscular atrophy. There is a degeneration of the cells of the anterior horn with atrophy of the horn itself, and a degeneration of the fibers of the direct and of the crossed pyramidal tracts (Fig. 795). The lesion in the horns is usually most pronounced in the cervical region. The extent of involvement of

[1] *Mingazzini, G.*, Family spastic paralysis of spinal type on a heredosyphilitic basis, Arch. Neurol. and Psychiat., 1921, v, 637.

[2] *Marie*, Lectures on Diseases of the Spinal Cord, London, New Sydenham Soc., 1895.

the motor tracts of the cord is extremely variable. The degeneration, which is the initial lesion, is accompanied by a replacement gliosis, and the picture presented on section of the cord is that of a sclerosis of the motor tracts and of the anterior horns. Quite frequently the sclerosis is not wholly confined to the motor tracts, but extends into the neighboring anterior and lateral tracts, especially in the cervical region. The degeneration in these tracts has been traced through the medulla, pons, and crus to the cortex, where changes have been observed in the large pyramidal cells. In the gray matter of the medulla are also found changes analogous to those in the anterior horns, consisting in degeneration of the cells of the motor cranial-nerve nuclei (hypoglossal, spinal accessory, pneumogastric, glossopharyngeal, and facial). The atrophy of the muscles innervated by these nerves gives the clinical picture of

FIG. 795.—AMYOTROPHIC LATERAL SCLEROSIS.

Degeneration of the crossed pyramidal and of the direct pyramidal tracts. In this case there was but little atrophy of the anterior horns. Very few cells, however, were present in the anterior horns and there was an increase in the connective tissue of the horns.

glosso-labio-laryngeal paralysis or progressive bulbar paralysis. The medullary lesion may occur without any corresponding lesion of the cord, thus giving rise to a bulbar paralysis without any spinal symptoms. The seat of the initial lesion, whether in the cell bodies in the cortex or in their axones, is as yet undetermined. The fact that disturbances of nutrition acting primarily upon the cell body are frequently most evidenced by changes in parts of the neurone farthest from the trophic center has already been mentioned. The muscle changes are those of a progressive muscular atrophy.

DEGENERATION OF THE PERIPHERAL SENSORY NEURONES. (*Tabes Dorsalis—Posterior Spinal Sclerosis—Locomotor Ataxia.*)

The essential lesion of tabes is a primary progressive degeneration of the peripheral sensory neurone system. As its older title indicates, the

clinical picture of locomotor ataxia had been attributed to a primary sclerosis of the posterior columns. This was not because in these columns was the only lesion, but because, owing to the close packing together here of the sensory axones, this lesion was the most conspicuous. The distribution of the lesion is coextensive with the peripheral sensory neurone system (page 1164). Any part of the system may be affected or the lesion may involve practically the whole system; again, the entire neurone may be affected, or only part of the neurone, or one part more than other parts. In general it may be said that it is the central process of the neurone, which enters the cord in the posterior nerve roots that shows the earliest and most extensive changes.

It is convenient to classify the lesions of tabes according to the anatomy of the peripheral sensory neurone system, as follows:

1. *The Peripheral Processes.*—(*a*) The sensory nerve endings. Changes of a degenerative character have been described in the sensory nerve endings of the skin, joints, and muscle. Especially well marked are lesions of the (sensory) muscle spindles which are almost constant.

(*b*) The peripheral nerves. Degenerations of the peripheral nerves are common. Like similar conditions due to toxic agents, they are usually referred to as a neuritis. The changes in both axones and medullary sheaths are, however, degenerative in character and similar to those of a Wallerian degeneration. The lesion is confined wholly to the sensory fibers, the motor fibers remaining intact. It is usually most pronounced in the smaller peripheral branches of the nerves. Degeneration of the optic nerve—so-called optic neuritis[1]—occurs in from ten to twenty per cent. of cases. Degeneration of the auditory[2] nerve and of the sensory fibers of the pneumogastric, glossopharyngeal, and trigeminus is of less frequent occurrence.

2. *The Cell Bodies.*—Marked degenerative changes in the cells of the spinal and analogous cranial ganglia and in the retina have been described. In a number of cases they have been found early in the disease. There is a reduction both in number and in size of the ganglion cells, with a replacement neuroglia hyperplasia. Chromatolysis with nuclear eccentricity has also been observed.[3]

3. *The Central Processes.*—(*a*) The sensory nerve roots, consisting as they do of the central processes of the spinal ganglion cells, show more or less complete degeneration. It is, in fact, in this part of the neurone that the earliest and most conspicuous changes are usually found. The extent and location of the degeneration vary. In the more common type of the disease—lumbar tabes—the earliest lesions appear in the posterior roots of the lumbar nerves. Only a few of the roots are at first affected, and only some of the fibers in these roots. With the progress of the disease more fibers are involved and the degeneration extends downward to the sacral roots and upward to those of the dorsal and cer-

[1] *Stargardt*, Ueber die Ursachen des Sehnervenschwundes bei Tabes und der progressiven paralyse, Arch. f. Psychiat., 1913, li, 711.

[2] *Knick, A.*, and *Zaloziecki, A.*, Ueber Acusticuserkrankungen im Frühstadium der Lues, inbesondere nach Salvarsan, Berl. klin. Wchnschr., 1912, xlix, 639.

[3] In Plate XV, 7, is seen a portion of a spinal ganglion from a case of advanced tabes. In addition to a degeneration of the cells present, there was a marked reduction in the number of cells in the ganglion.

vical nerves. In specimens stained by Weigert's method the contrast between the darkly stained anterior root fibers and the almost unstained posterior root fibers is often marked.

(*b*) The spinal cord. On removing the cord in a case of advanced tabes, certain changes are usually apparent to the naked eye. The pia mater between the two posterior horns is apt to be thickened, of a dull appearance, and adherent to the cord. This, in contrast to the normal condition of the rest of the pia, gives the effect of a narrow band extending the length of the cord. The posterior columns may be depressed, of a grayish color, and firmer than the rest of the cord. On section the contrast between the posterior columns and the rest of the white matter of the cord is often very distinct. In cords removed from patients dying during the earlier stages of the disease there are often no macroscopic lesions.

FIG. 796.—TABES DORSALIS.
Cervical region, showing an early stage of the lesion.

The microscopic appearances vary, depending on the stage, extent, and location of the lesion (Fig. 796).

In a case which comes to autopsy early in the disease the appearance of the lesion differs from that in a case of advanced tabes. As already noted, the most marked changes are in the posterior columns. In the more common type of the disease in which the degeneration begins in the lumbar region, sections of the cord at this level show certain quite well-defined areas of degeneration. The zone of Lissauer early shows marked degenerative changes. This zone extends across the entering fibers of the posterior root which divide the zone into two parts. The degeneration of the outer part has been wrongly described by some writers as a lateral-column degeneration. It will be remembered that these fibers are short fibers which have entered the cord in the nearest posterior root. Degeneration usually appears early in that part of the column of Burdach which borders the posterior horn. The column of Goll varies as to the extent of involvement. In many cases it is only slightly affected, in others the degeneration is marked. As the fibers of this column

come mainly from the last lumbar and first two sacral segments, it is seen that its condition depends entirely upon the integrity of these roots. The fibers of the posterior columns have two sources: (1) entering fibers of the posterior roots; (2) fibers from cells in the gray matter of the cord. The latter are situated mainly in a narrow strip behind the posterior commissure and in the median oval area of Flechsig. These fibers are unaffected in tabes.

The degenerations seen in sections of the dorsal and cervical cord in lumbar tabes are dependent upon an ascending degeneration of the fibers affected below. The columns of Goll are thus usually affected, while the columns of Burdach are often only slightly involved. If at any level of the cord degenerated root fibers enter the cord, there results

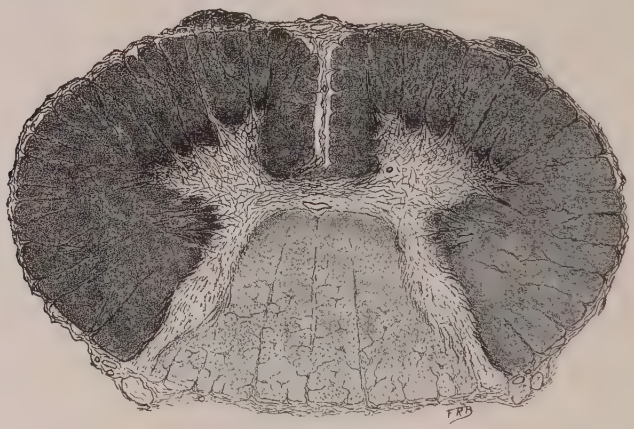


Fig. 797.—Tabes Dorsalis.
Cervical region, showing an advanced stage of the lesion.

a degeneration in the zone of Lissauer and in the band of fibers lying along the posterior horn at that level.

Rarely the tabetic process begins in the cervical region. In these cases section of the cervical cord shows not only normal endogenous fibers, but a normal condition of the column of Goll and of such part of the column of Burdach as originated below the level of the lesion. Sometimes the dorsal roots are affected with the cervical. In cervical tabes the cord below the affected region is normal, while above is the lesion of an ascending degeneration. The lesion may in any case be asymmetrical, one root of a segment being affected while the other remains normal.

In cases of advanced tabes (Fig. 797) there are often almost no normal nerve fibers in the posterior columns, the columns of Goll, of Burdach, and of Lissauer presenting little but dense fibrous tissue. The posterior fissure may be completely obliterated. There usually remain, however, evén in advanced tabes, undegenerated fibers bordering the posterior commissure and the adjacent parts of the posterior horns. The median area of Flechsig also remains intact. As already noted, these fibers are endogenous.

The microscopical appearance of the degenerated areas varies with the stage of the process (Fig. 798). The new connective tissue may be at first quite cellular; later the fibrillar elements predominate and the tissue becomes dense and firm. Of the nerve roots some have disappeared, others show degeneration of their medullary sheaths and axis-cylinders. Some few normal fibers are usually present even in advanced sclerosis. The blood-vessels often have thickened walls and may show lymphoid and plasma cells in the Virchow-Robin spaces. There may be corpora amylacea and fat globules, the latter either free or collected in cells. The pia is infiltrated with lymphoid and plasma cells and, in the chronic stages of the disease, is rich in fibrous tissue.

The lesion of tabes is not, however, confined to the posterior columns. The fibers of these columns are constantly sending collaterals and terminals into the gray matter. Most of these pass into the posterior horns,

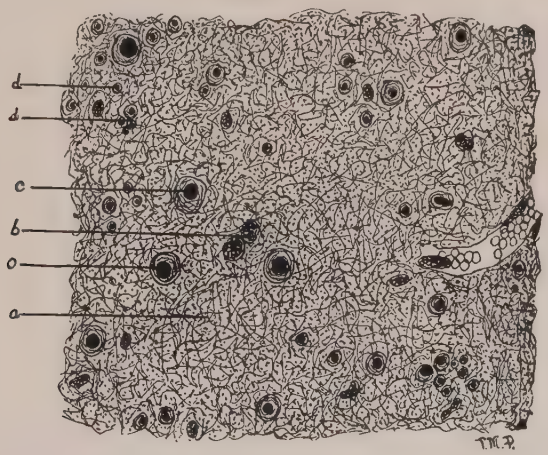


FIG. 798.—POSTERIOR SPINAL SCLEROSIS. (TABES DORSALIS.)
A portion of sclerosed area in the posterior columns of the spinal cord. *a*, New-formed connective tissue; *b*, blood-vessels; *c*, nerve fibers; *d*, atrophied nerve fibers.

an especially well-marked group entering Clarke's cell column. The posterior horns are therefore usually smaller than normal, with a marked reduction in the number of fibers entering them from the posterior columns, while the columns of Clarke show a diminution in the number of delicate fibrils which normally surround the ganglion cells.

Changes have also been described in the spinal root of the fifth cranial nerve and in the fasciculus solitarius which consists of afferent fibers of the vagus and glossopharyngeal nerves. These fibers are analogous to those of the posterior columns, and the changes in them are similar.

Degenerations of a secondary character may occur in those systems of neurones which are more or less dependent upon the peripheral sensory neurone system for their impulses. Thus the cells of Clarke's column may be affected, with resulting degeneration of their axones which make up the direct cerebellar tract. This degeneration extends through the restiform body to the termination of the tract in the cerebellum.

The cells of the gray matter whose axones form Gowers' tract may be degenerated with consequent degeneration of the fibers of this tract. In the medulla the cells of the nucleus gracilis and nucleus cuneatus may be affected, thus determining an ascending degeneration along the tracts followed by their axones. Degeneration of the cells of the anterior horns of a similar character has been seen. These changes in the anterior-horn cells have been accepted by some investigators as explanatory of the various trophic disturbances which so frequently occur during the course of tabes. Similar changes have been found in the nuclei of two of the motor cranial nerves, the oculomotor and the hypoglossal. Others ascribe the trophic disturbances to a peripheral neuritis. Marie[1] describes a case interesting in this connection, in which there was marked hemiatrophy of the tongue with distinct changes in both main and accessory nuclei of the hypoglossal nerve on the same side, the opposite nuclei being normal. Similar cases of tabes, with laryngeal crises in which there were pronounced degenerative changes in the pneumogastric nucleus and in the ascending root of the glossopharyngeal, have been reported. Changes have been described in the cells of the cerebral cortex. They are similar to those found in dementia paralytica, but less marked.

Although various hypotheses have been advanced in explanation of the tabetic lesion, present knowledge favors the view that tabes is due to a degeneration of the posterior spinal roots.[2] Nageotte[3] accounted for the posterior column degeneration on the basis of an inflammatory process of the radicular nerve, which includes both sensory and motor roots and extends mesially from the spinal ganglion to the spinal cord. The motor fibers escape because of their great resistance; the sensory fibers are more delicate and degenerate. The inflammatory process involves the epineurium, perineurium, and endoneurium. Obersteiner and Redlich[4] claimed that the posterior roots, in passing through the pia lining the spinal cord, were compressed partly by the inflammatory exudate in the pia and partly by the shrinking pia and by pressure from the sclerosed vessels. Later, Redlich,[5] in his explanation of the tabetic process, admitted the possibility of a toxic factor acting upon the intramedullary portion of the posterior roots. Spiller[6] emphasized the meningeal lesions in tabes and insisted that tabes should be regarded as a cerebrospinal disease. Bresowsky,[7] in an exhaustive study of a large number of cases, arrived at the conclusion that the extensive inflammatory meningeal process serves as a toxic agent on the posterior roots. Schaller[2] concluded from his pathological material that in tabes there is probably a primary syphilitic pial and arachnoid meningitis which is the basis for the subsequent tabes. The subacute inflammatory meningitis produces root degeneration by direct extension of the meningeal lesions to the nerve roots, causing a meningo-radiculitis, by pressure constriction from the sclerosed meninges, by toxic products engendered by this inflammation, and by increased spinal fluid, these factors working alone or in conjunction with one another. Occasionally one finds anterior root degeneration changes giving a picture of amyotrophic tabes.[8] Tabes is now regarded as one of the many anatomical changes caused by the Treponema pallidum. The disease is ten times as frequent in males as in females.

[1] *Marie*, Lectures on Diseases of the Spinal Cord, New Sydenham Soc., London, 1895.

[2] *Schaller, W. F.*, Pathogenesis of tabes dorsalis, Arch. Neurol. and Psychiat., 1919, i, 749.

[3] *Nageotte, J.*, La lésion primitive du tabes, Bull. de la soc. anat. de Paris, 1894, viii, 808.

[4] *Obersteiner, H.*, and *Redlich, E.*, Ueber Wesen und Pathogenese der tabischen Hinterstrangsdegeneration, Arbeiten a. d. Inst. f. Anat., u. Physiol. d. Centralnervensystems, Wien, 1894. (Abstr. Neurol. Centralbl., 1894, xiii, 454.)

[5] *Redlich, E.*, Die Pathologie der tabischen Hinterstrangserkrankung, Jena, 1897.

[6] *Spiller, W. G.*, Pathology of tabes dorsalis, Internat. Med. Mag., 1897, vi, 321.

[7] *Bresowsky, M.*, Über die Veränderungen der Meningen bei Tabes und ihre pathogenetische Bedeutung, Arbeit. a. d. Neurol. Inst., Wien, 1912–13, xx, 1.

[8] *Wilson, S. A. K.*, Tabetic amyotrophy, Rev. Neurol. and Psychiat., 1911, ix, 401

Ataxic Paraplegia—Subacute Combined Sclerosis.—This is a disease of uncertain etiology, in which there are degenerative changes in both motor and sensory neurone systems (Fig. 799). The tracts usually involved are those of Burdach and of Goll, the direct cerebellar tracts, and the crossed pyramidal tracts. Less commonly the degeneration extends to the tracts of Gowers and to the direct pyramidal tracts. It seems probable that the lesion in the cord is not always the expression of the same pathological process, and that in many cases it is not the result of a true systemic degeneration. In perhaps the minority of cases the lesion corresponds to the tract systems of the cord and probably represents a combined sensory-motor degeneration. Such are those rare cases in which the degeneration affects all of the above-mentioned tracts. The pia is thickened; the vessels are sclerotic; and the cord, owing to the atrophy, is shortened. The lesion affects the myelin principally, and the axones become involved only late in the disease, giving a picture of Wallerian degeneration. There is an active glial proliferation, and active phagocytic glia cells are present which remove the degenerating myelin. The adventitial spaces of the vessels are filled with phagocytic cells. The degeneration is most marked at the periphery of the cord, which, on cross section, presents many vacuoles in this region, giving it a cribriform appearance.[1]

According to Dejerine, the appearance of a combined system disease may be induced by the chronic meningitis, which exists over the posterior columns in tabes, extending forward over the direct cerebellar tract, the productive inflammation finally spreading to this tract and to the crossed pyramidal. In these cases that part of the

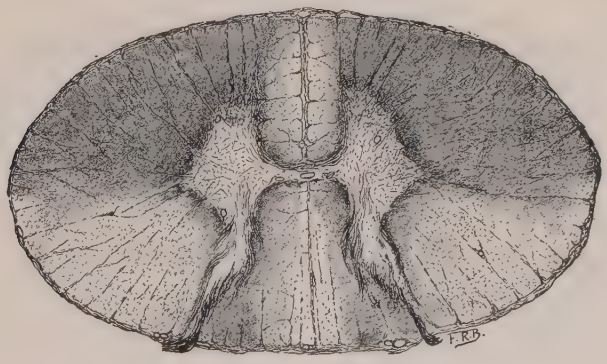


Fig. 799.—Combined System Disease.

Showing degeneration and sclerosis in the columns of Goll, the direct and the crossed pyramidal tracts, and the direct cerebellar tract.

latter tract which lies deepest, i.e., close to the gray matter, usually remains uninvolved. Marie lays particular stress upon the arterial systems of the cord as the prime factor in many cases, calling attention to the fact that the lesion, as it is most commonly found, coincides almost exactly with the distribution of the posterior spinal arteries. By others the lesion is ascribed to a multiple sclerosis, the restriction of the degeneration to definite tracts being only apparent. It is possible that in some cases the pathological picture of a combined sclerosis may be due to secondary

[1] *Hassin, G. B.*, Histopathological findings in two cases of subacute (combined) cord degeneration, Med. Record, 1917, xci, 885.

degeneration following myelitis. It is obvious that authors differ as to its exact classification. It is most frequently encountered in chronic wasting diseases, pernicious anemia, and lead and ergot poisoning.

A subacute type of combined system degeneration has been described by Russell.[1] The degeneration involved the same tracts affected in the more chronic type, and was often very extensive at some levels of the cords studied, there being only a thin layer of normal fibers covering the gray matter.

Under the name of diffuse degeneration of the spinal cord, a somewhat similar condition has been described,[2] the question as to the systemic nature of the process being left open.

Traumatic and Sclerotic Cord Lesions.

Chronic Interstitial Myelitis.—Under this heading are embraced a variety of lesions which probably differ from one another somewhat in the nature of the changes involved, but more in the seat of the disease. We shall consider without special classification the most important forms.

Chronic Transverse Myelitis.—In certain cases of pressure on the spinal cord from a tumor or from displacement of the bones of the vertebral column, etc., the cord, instead of becoming softened or undergoing acute inflammatory changes, becomes the seat of a localized formation of new connective tissue with consecutive atrophy of more or less of the nerve elements in the gray and white matter. The cord becomes in this way harder, and sometimes shrunken at the seat of lesion, and gray in color. This change may be followed by ascending and descending degeneration.

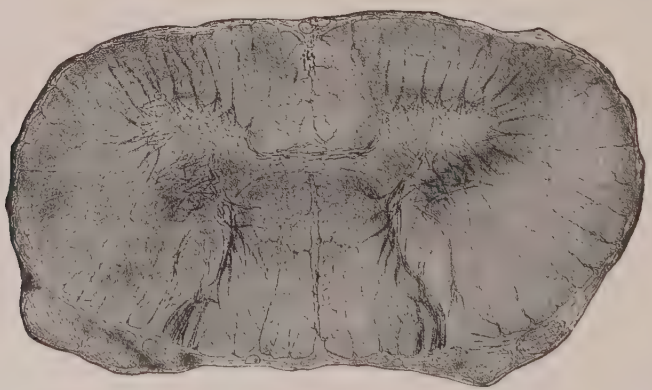


Fig. 800.—Multiple Sclerosis in the Spinal Cord.
Showing irregular areas in which there are atrophy of the nerve fibers and their replacement by connective tissue.

Chronic Disseminated Myelitis—Multiple Sclerosis.[3]—This lesion, similar in its nature to multiple sclerosis of the brain, often occurs with it. It consists in the formation, in more or less numerous scattered, circumscribed areas, of new connective tissue, derived from the neuroglia.

[1] *Russel, Batten,* and *Collier,* Brain, London, 1900, xxiii, 39.
[2] *Putnam* and *Taylor,* Jour. Nerv. and Ment. Dis., 1901, xxviii, 1, 74.
[3] *Dawson, J. W.,* and *Bruce, A.,* Histology of disseminated sclerosis, Rev. Neurol. and Psychiat., 1917, xv, 47; xvi, 12; *Klingman, T.,* Histogenesis of multiple sclerosis, Arch. Neurol. and Psychiat., 1919, 39, 193.

Primarily it is a disease of the myelin sheaths. At first these break up into fat droplets which are stained black by the Marchi stain. Fat granular glia cells appear and remove the degenerating droplets of myelin. The fiber-forming glia cells then make their appearance and replace the degenerated myelin with glia fibers which eventually form the glia sclerosis or glia scars. The degeneration of the myelin sheath is an acute process, while the formation of sclerotic plaques is chronic in nature.[1] The new connective tissue consists of the characteristic branching neuroglia cells, surrounded by a more or less dense network of fine fibrillæ, many, if not most, of which seem to be branches of the neuroglia cells. Corpora amylacea and sometimes fat droplets, either free or contained in cells, may be present in the sclerosed areas.

The areas of sclerosis may involve both gray and white matter, and may be very small or large (Fig. 800). If very small or in early stages of formation, they may not be recognizable by the naked eye, but when visible they are grayish, translucent, and firmer than the surrounding tissue, and may or may not present a depressed surface; they sometimes project above the general level. The cause of this as of all other forms of so-called idiopathic interstitial myelitis is very obscure. As noted in multiple sclerosis in the brain, secondary degenerations are rare, and probably for the reason there given. The degeneration does not follow along the tracts of the cord, and sections of the cord only a few millimeters apart will show different areas of degeneration and sclerosis.

Syringomyelia.[2]

This lesion of the spinal cord consists in the production of gliomatous tissue in the vicinity of the central canal, and its subsequent partial disintegration with the formation of one or more cavities within the substance of the cord (Fig. 813). The cavities, which are filled with fluid, vary greatly in size, shape, and extent, and, while usually situated in the central region of the cord, may involve the anterior and posterior cornua and invade the posterior columns. There may be two communicating cavities, and these may, but usually do not, open into the central canal. The longitudinal extent of these cavities varies greatly. The lower cervical and upper dorsal regions are most frequently involved. The cavity is usually lined with tissue somewhat denser than that which makes up the bulk of the tumor. The gliomatous tissue which forms the basis of the lesion in syringomyelia probably originates from the layer of neuroglia or ependyma which surrounds or extends away from the central canal. The ependymal lining of the central canal is reduplicated and broken in places. There is an increase in the number of capillaries, and the pia is definitely hyperplastic. Small hemorrhages and foci of myelitis may be found. The disease may last for years; it is principally a lesion of the glia, which may be regarded as being deficient

[1] *Spiller, W. G.*, Subacute form of multiple sclerosis, Arch. Neurol. and Psychiat., 1919, i, 219; *Marinesco, G.*, Étude sur l'origine et la nature de la sclérose en plaques, Rev. Neurol., 1919, xxvi, 481.

[2] *Hassin G. B.*, Histopathology and histogenesis of syringomyelia, Arch. Neurol. and Phychiat., 1920, iii, 130.

from early life. Anesthesia to pain and temperature, but not to touch, and trophic disturbances are prominent symptoms.

Syringomyelia is frequently mistaken for hydromyelia, which is a congenital malformation, in which the longitudinal cavity in the cord is at some period lined with epithelial cells. Syringomyelia has also been confused with hematomyelopore.

There seems, furthermore, to be a class of lesions of the cord, usually classed as syringomyelia, in which cavities of various forms coexist with a tumor in the vicinity of the central canal. But these cavities appear to be formed not by a breaking down of the tumor tissue, but in some other way as yet little understood.

Friedreich's Ataxia. (*Hereditary Ataxia.*)

This disease, while often referred to as hereditary ataxia, has more of a family than of a distinctly hereditary character.[1] Clinically, the disease is characterized by ataxia, beginning in the lower limbs and gradually ascending so that even speech may be interfered with. Paralysis and contractions are the final results. Its pathology is marked by a decrease in the size of the spinal cord, the diameter of which is often not more than three-quarters that of the normal cord. Degeneration of the columns of Goll is usually quite complete. Less marked degeneration is found in the columns of Burdach, in the direct cerebellar and in the crossed pyramidal tracts. The marginal tract of Lissauer may or may not be affected. In the posterior horns and in the columns of Clarke the condition resembles that in tabes. There may be atrophy of the cerebellum. An extensive gliosis exists in the diseased areas.

Marie notes in addition, atrophy and disappearance of the cells of Clarke's column. Blocq and Marinescu[2] describe degeneration of the posterior root fibers similar to that found in tabes. Friedreich[3] and Rütimeyer[4] find atrophy of the anterior horn cells. The determining cause of the disease and the nature of the morbid process are as yet undetermined. It seems probable that the condition of the cord may be more properly considered an abnormality of development rather than a degeneration.

Cerebellar Ataxia.

Atrophy of the cerebellum was noted as sometimes occurring in Friedreich's ataxia. In that disease, however, the cord lesion was most marked. In cerebellar ataxia the lesion of the cord is slight or absent, the chief lesion being an atrophy of the cerebellum. This atrophy is accompanied by little or no sclerosis, the organ being simply smaller than normal.[5] Whether cerebellar ataxia is to be considered as an entity separate from the preceding is doubtful.[6]

[1] *Lloyd, J. H., and Newcomer, H. S.*, a case of Friedreich's ataxia, Arch. Neurol. and Psychiat., 1921, vi, 157; *Pfeiffer, J. A. F.*, a case of hereditary ataxia (Friedreich) with anatomic findings, ibid., 1922, vii, 341.

[2] *Blocq, P.*, and *Marinescu, G.*, Compt. rend. de la Soc. de Biol., 1890, ii, 118.

[3] *Friedrich, N.*, Virchows Arch., 1881, lxxxvi, 421.

[4] *Rütimeyer, L.*, Virchows Arch., 1887, cx, 215.

[5] *Londe*, Hérédo-ataxie-cérébelleuse, Paris, 1895.

[6] See *Oppenheim*, Lehrb. d. Nervenkrankh., 6th ed., Berlin, 1913, p. 240.

Acute Inflammation of the Brain. (*Encephalitis.*)

Acute Encephalitis.—Inflammatory processes in the nervous system, whether of an exudative or of a productive type, are frequently consecutive to or coincident with the more severe forms of degeneration or other lesions, thus making differentiation of the processes often extremely difficult. It has been already mentioned that the brain tissue about hemorrhages and areas of embolic and thrombotic softening may undergo inflammatory changes leading to the formation of new connective tissue. There is a class of cases in which localized areas of the brain undergo softening, with more or less extravasation of red and white blood-cells and hyperemia, so that the softened material consists, as seen under the microscope, of detritus of brain tissue in a condition of fatty degeneration, often with more or less pus cells and pigment. When such areas are red in color from intermingled blood-cells or pigment, the condition is called *red inflammatory softening*. When fatty degeneration prevails, and the red blood-cells or their derivatives are not abundant, the softened area looks yellow or yellowish-white, and this is often called *yellow inflammatory softening*. The origin of these processes is very obscure and their inflammatory nature not well defined.

Abscess of the Brain.—Small multiple abscesses of the brain may occur in pyemia. Large abscesses of the brain are usually single; they may attain a large size. They are most frequent in the cerebral and cerebellar hemisphere, rare in the basal ganglia, the pons, and the medulla oblongata.[1]

There may be an irregular cavity containing thin pus and softened brain tissue.[2] The walls of the cavity are ragged and infiltrated with pus, and outside of the walls is a zone of edematous and softened brain tissue. If the abscess be near the pia mater, meningitis may follow; if it be near the lateral ventricles, it may rupture into them; if it be near the sinuses of the dura mater, it may induce thrombosis. An abscess may in time become inclosed in a capsule of connective tissue. In acute suppuration the abscess is not encapsulated, and the suppurative process is very diffuse. The ganglion cells undergo all gradations of degeneration, from mere cloudy swelling and chromatolysis to complete disintegration. The glial elements undergo proliferation. The blood-vessels are congested, and the Virchow-Robin spaces are filled with lymphocytes and plasma cells. Thrombosed vessels are also present.

In the chronic suppurative processes,[3] the abscess is walled off from the rest of the brain tissue by a firm dense fibrous capsule. The abscess is composed of a central necrotic area, an encapsulating dense membrane, and an outer zone of engorged vessels. The encapsulating membrane has three distinct layers, an inner collagenous layer, a middle delicate layer containing numerous fibroblasts, plasma cells, connective tissue fibers,

[1] For a study of acute encephalitis and brain abscess, see *Southard, E. E.*, Osler and McCrae, Modern Medicine, Philadelphia, 1915, v, 359.

[2] *Essick, C. R.*, Pathology of experimental traumatic abscess of brain, Arch. Neurol. and Psychiat., 1919, i, 673.

[3] *Hassin, G. B.*, Histopathology of brain abscess, Arch. Neurol. and Psychiat., 1920, iii, 616.

and blood-vessels, and an outer layer containing many collagen fibers, plasma cells, fibroblasts and distended blood-vessels.

Abscess of the brain is most frequently secondary to chronic suppurative otitis (42.5 per cent., Gowers), much less frequently to acute otitis. With the otitis there may also be caries of the temporal bone, suppuration of the mastoid cells, and inflammation of the dura mater. The abscess is usually situated deep in the brain, commonly in the temporosphenoidal, the frontal, the occipital or the parietal lobes, or in the cerebellum; rarely it is continuous with the inflamed dura mater and bone. Abscess may follow chronic lesions in the orbit, caries of various parts of the cranial bones, and sinus infections.

Abscess of the brain frequently follows traumatism, blows, or falls on the head. Such injuries may not damage the skull, or may produce fractures or necrosis. There is often a considerable interval between the time when the injury is inflicted and the development of the symptoms.

When the cranial bones are uninjured the abscess is usually deep in the brain; when there is necrosis of the bones the abscess may be superficial; when the bones are fractured the abscess may be either superficial or deep. The abscess develops rarely in the opposite side of the brain.

In acute exudative meningitis from various excitants there may be an infiltration of the brain with leucocytes; this may be especially marked in the perivascular tissue and around the ganglion cells.

Acute Disseminated Encephalitis,[1] hematogenous in character, may develope during the progress of an infectious disease. It is most common in infective endocarditis, in pyemia, and in cerebrospinal meningitis. It may be associated with acute anterior poliomyelitis, pneumonia, and epidemic influenza. The lesion consists of disseminated foci of inflammation, or minute multiple abscesses. Some of these are microscopic in size, others may be seen with the naked eye. The smallest show simply small lymphocytic and plasma-cell infiltration of the walls of one or more small vessels and of the surrounding tissue. The larger spots, which undoubtedly take origin in the same way, are seen to be softer than the rest of the tissue, and resemble red or yellow softening, according to the amount of red blood-cell extravasation. Congestion is usually marked. There may be distinct hemorrhages. Degenerative changes with disintegration of the exudate usually set in and determine destructive changes in the neighboring neurone and neuroglia elements. The ganglion cells show cloudy swelling, chromatolysis, and eccentrically situated nuclei. Neuronophagy is also present. At the periphery of one of these abscesses the neuroglia, instead of being in a degenerating condition, usually shows proliferation. The more minute inflammatory foci may undergo complete resolution with absorption of the exudate. In the larger abscesses there may be absorption of the exudate and of the products of degeneration, and a replacement neuroglia hyperplasia, ultimately resulting in a sclerotic patch.

[1] Under the head of "Acute Parenchymatous Encephalitis" has been described a lesion of the ganglion cells without vascular or interstitial changes. These lesions are the result of toxemias of either endogenous or exogenous nature. They are more properly classed as parenchymatous degeneration.

Suppurative encephalitis may occur as a result of traumatism or from extension of suppurative meningitis.

A form of encephalitis which has been designated acute non-suppurative hemorrhagic encephalitis, has been described.[1] The lesion consists in the occurrence of multiple hemorrhagic, inflammatory foci, which are non-suppurative, and which are accompanied by leucocytic infiltration. These foci may occur in any part of the brain, but are most numerous in the white matter of the brain and basal ganglia. Some of these hemorrhages may be quite large.

ACUTE EPIDEMIC ENCEPHALITIS (Encephalitis Lethargica.)[2]

This is an acute epidemic disease which has only recently been recognized. The symptoms are extremely variable as is the course of the disease. Many mild cases unquestionably occur which pass undiagnosed. In other instances the patient dies in a few days with symptoms of an acute encephalitis.

Clinically some eight or ten varieties have been distinguished. The most general symptoms are marked asthenia with prolonged somnolence. Palsy of the cranial nerves is a frequent accompaniment. Some of the cases resemble poliomyelitis; others are maniacal. In the late stages the syndrome resembling paralysis agitans may appear. The lesions are as variable as the symptoms but in the encephalitic type certain changes are fairly constant.[3] On gross examination the brain appears congested and the vessels markedly engorged. The dura mater is normal. The pia arachnoid is edematous, and may present minute hemorrhages. The brain stem shows the greatest amount of congestion. Microscopically, the brain stem, basal ganglia, pons, and medulla are the regions of the greatest inflammatory reaction, although any part of the brain may be intensely involved. The cerebellum is least affected. There is marked infiltration of the Virchow-Robin spaces with lymphocytes and, to a lesser degree, with plasma cells and larger cells of mesodermic origin. Thrombosis of the vessels in the acute stage is very rare. Throughout the parenchyma, and apparently without any connection with perivascular exudation, there are masses of inflammatory cells, mostly lymphocytes and, to a considerably lesser extent, plasma and endothelial cells. Hemorrhagic areas are abundant especially near blood-vessels. The endothelial cells of the blood-vessels are swollen and appear to proliferate, as is manifested by the numerous mitotic figures in these cells. The nervous tissue proper, both the ganglion cells and the glia cells, are relatively little involved considering the intensity of the general inflammatory process. In the regions of greatest inflammatory reaction, the ganglion cells may show

[1] *Putnam*, Jour. Nerv. and Ment. Dis., 1897, xxiv, 1 (bibl.).

[2] A useful collection of clinical reports will be found in *Tilney, F.*, and *Howe, H. S.*, Epidemic Encephalitis, New York, 1920.

[3] *Bassoe, P.*, and *Hassin, G. B.*, Histopathology of epidemic lethargic encephalitis, Arch. Neurol. and Psychiat., 1919, ii, 24; *Buzzard, E. F.*, and *Greenfield, J. G.*, Lethargic encephalitis; its sequelæ and morbid anatomy, Brain, 1920, xlii, 305; *Schroeder, P.*, Encephalitis und Myelitis, Monatschr. f. Psychiat. u. Neurol., 1918, xliii, 146; *Macnalty, A. S.*, The morbid histology, bacteriology and experimental pathology of encephalitis lethargica, Brit. Jour. Exper. Path., 1921, ii, 141 (bibl.).

cloudy swelling, chromatolysis, eccentrically situated nuclei, and even neuronophagy. In these areas, there is considerable neuroglia proliferation especially of the small round glia cell type. There is considerable edema present, and under the microscope this is evident as poorly staining homogeneous areas within the parenchyma. The spinal cord, especially in the cervical region, presents similar findings, but to a markedly less degree. Strauss and Loewe have recovered a filterable virus from their pathological material and by inoculation of this virus into rabbits have been able to reproduce both the clinical and the pathological pictures of the disease.[1] For the Parkinsonian syndrome see page 1195.

Acute Inflammation of the Spinal Cord. (*Acute Myelitis.*)

Inflammation in the spinal cord is quite analogous to inflammation in the brain.

Acute Disseminated Myelitis[2] runs a rapid course and proves fatal in a short time.[3] The inflammation may involve nearly the whole length of the cord, but is usually more intense in some places than in others. The cord is swollen and congested, it is infiltrated with pus cells, the connective tissue is swollen, and there is degeneration of the nerve elements proper.[4]

More frequently an acute myelitis is localized. It involves but a small portion of the length of the cord, while laterally it may completely cross it, and is hence spoken of as a *transverse myelitis.* When the cord is removed and laid upon the table, if the lesion is marked, a flattening of the cord at its seat may be observed; or when the finger is passed gently along the organ, the affected segment will be found softer than the rest of the cord, sometimes almost diffluent. When a section is made through the affected portion, the nerve tissue may appear white or red or yellowish or grayish.

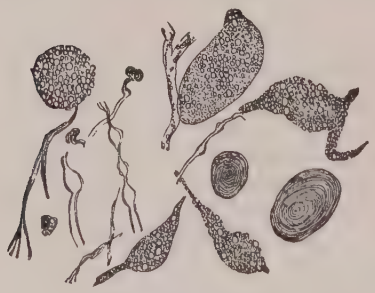


Fig. 801.—Degenerated Tissue from Acute Myelitis.

Microscopical examination shows different appearances, depending upon the stage of the degenerative or inflammatory process.[5] There may be much blood, or, if the lesion has existed for some time, blood pigment; also fragments of more or less degenerated nerve fibers and ganglion

[1] *Lœwe, L.*, and *Strauss, I.*, Studies in epidemic (lethargic) encephalitis, Jour. Inf. Dis., 1920, xxvii, 250.

[2] Acute parenchymatous myelitis, like its analogue in the brain, is a lesion of the ganglion cells, and is more properly classed as a degeneration. Embolic and thrombotic softenings are more rare in the cord than in the brain, and are necessarily much more restricted in extent. When of an inflammatory character they resemble the similar brain lesion and are red or yellow according to the amount of extravasation. For bibl. see *Schmaus, H.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix[1], 313.

[3] *Morris, L. M.*, and *Jacobson, V. C.*, Acute ascending myelitis of infectious type, Arch. Neurol. and Psychiat., 1921, vi, 509.

[4] *Hassin, G. B.*, Histopathologic changes in five cases of myelitis, Med. Record, 1916, xc, 619.

[5] *Bassoe, P., and Hassin, G. B.*, Myelitis and myelomalacia, Arch. Neurol. and Psychiat., 1921, vi, 32.

cells (Fig. 801), myelin droplets, free fat granules, larger and smaller cells filled with fat granules (Gluge's corpuscles), pus cells, granular matter, neuroglia cells, and sometimes corpora amylacea. The various proportions of these elements give rise to the different gross appearances which the diseased part presents. In earlier stages of the lesion the blood-vessels may be dilated, the nerve fibers and cells swollen; or the walls of the blood-vessels may be thickened or fatty, or surrounded by a sheath of leucocytes and cells derived from the connective-tissue cells of the adventitia.[1] There is a marked glia reaction The large fat granular glia cells absorb the degenerating myelin and transport it to the neighborhood of mesodermic tissue. They almost replace the degenerating areas. The advential spaces are distended with cellular infiltration. The pia spaces are also distended with leucocytes, erythrocytes, and plasma cells. The subarachnoid space contains considerable débris. There is a large amount of proliferation of the endothelial cells.

The lesion is apt to commence in the gray matter or at its edge, and then extend first laterally and afterward upward and downward.

In a certain number of cases the degenerated material may be absorbed and a cicatrix or cyst formed. After the least extensive forms of the lesion there may be a restoration of the functions of the cord.

Secondary degeneration, both ascending and descending, may occur in this form of myelitis, varying in extent according to the size of the primary lesion. The terms *central myelitis*, *peripheral myelitis*, and *unilateral myelitis*, are sometimes used to designate localizations of the lesion.

Acute Poliomyelitis.—This name is applied to a group of cases of acute infectious disease characterized by a variety of clinical symptoms,

Fig. 802.—Acute Anterior Poliomyelitis.

Death seven weeks after onset. Showing gliomatous tissue in both horns, with cavity formation in one of them.

the most evident of which are due to changes in the anterior horn cells of the spinal cord.[2] For this reason, the disease is sometimes called *acute anterior poliomyelitis*. Because it often appears in children, it is

[1] *Lotmar, F.*, Beiträge zur Histologie der acuten Myelitis und Encephalitis, sowie verwandter Prozesse, Nissl and Alzheimer Histologische und Histopathologische Arbeiten, Jena, 1913, vi, 245.

[2] *Peabody, Draper,* and *Dochez*, A clinical study of acute poliomyelitis, Monograph No. 4, Rockefeller Inst., New York, 1912.

known also as *infantile paralysis;* and is also called *Heine-Medin's disease,* from Heine, who, in 1840, first differentiated the condition from similar neurological affections, and Medin, who published in an important monograph the results of his observations on the great Swedish epidemic of 1887.

While the spinal type of the disease is the most frequent, encephalitic, cerebellar, bulbar, polyneuritic, and meningitic forms are now recognized; and it is probable that there are many abortive cases in which the nervous system escapes damage. Wickman[1] was the first to recognize from clinical observation that the disease was of an infectious nature, and Landsteiner and Popper[2] first successfully transmitted the disease to monkeys. Shortly afterward, Flexner and Lewis confirmed their work and greatly extended our knowledge of the nature of the disease. Noguchi finally isolated the organism (see page 338).

In the acute stage of the disease, evidences of nasopharyngeal inflammation are often found, the spleen is occasionally enlarged, and

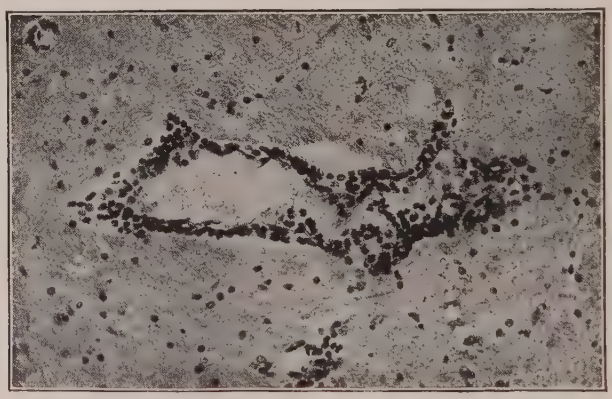


Fig. 803.—Perivascular Infiltration in Cord in Case of Acute Anterior Poliomyelitis. Preparation of Dr. Simon Flexner.

moderate hyperplasia of the lymphoid structures occurs. The cerebrospinal fluid is clear and increased in amount, later becoming opalescent, and contains a large number of lymphocytes. The pia is congested, the spinal cord is hyperemic, the congestion being especially noticeable in the gray substance. Dilated vessels and minute capillary hemorrhages are not infrequent. There is often extensive edema of all the tissues of the spinal cord. In addition to the cord changes, there may be edema and hyperemia of the brain substance with minute hemorrhages, but usually the gross alterations in the brain are not at all evident to the naked eye. In late cases, the spinal cord may show macroscopic alterations, even so extensive as to lead to an asymmetrical distortion from atrophy of the anterior horn. Areas of softening may occur in the anterior horn (Fig. 802). The nerve bundles arising from the affected area are diminished in size.

[1] *Wickman, I.,* Acute Poliomyelitis, Nerv. and Ment. Dis., Monograph Series, No. 16, NewYork, 1913 (trans. of article in Lewandowsky, Handb. d. Neurologie, Berlin, 1911, ii, 807 (full bibl.).

[2] *Landsteiner* and *Popper,* Ztschr. f. Immunitätsforsch., Orig., 1909, ii, 377.

Microscopically, there is usually a round-cell infiltration in the pia, the cells being most frequently lymphocytes; polyneuclears, however, are not rare; plasma cells are very scanty. This infiltration is often espe-

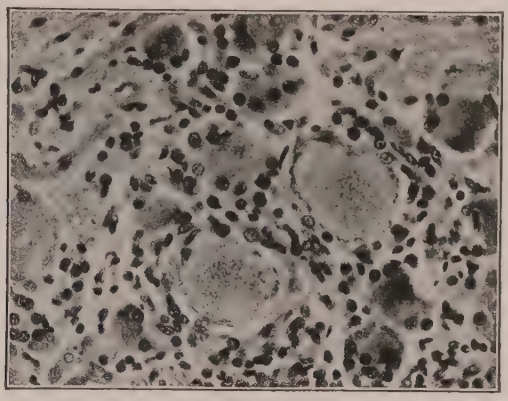


Fig. 804.—Ganglion Cell Lesions in Acute Anterior Poliomyelitis. Preparation of Dr. Simon Flexner.

cially marked about the vessels and in the region of the active lesions in the anterior horn. The dura usually escapes involvement. In the spinal cord the veins and capillaries are often greatly distended with blood; thrombi are rare. Minute hemorrhages are not at all infrequent

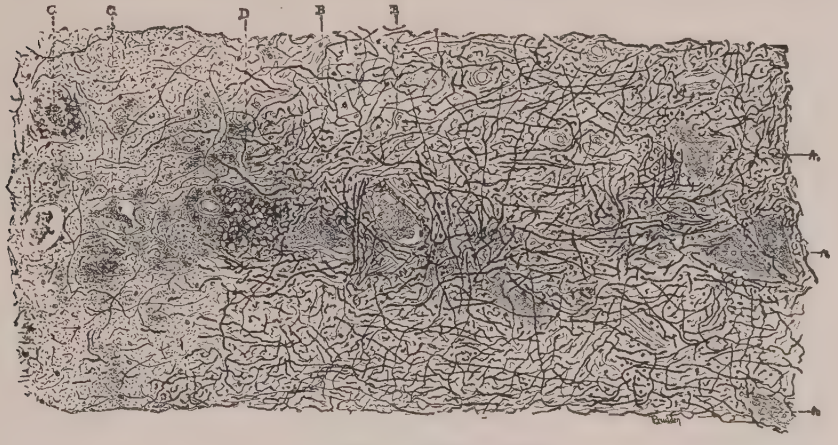


Fig. 805.—Poliomyelitis Anterior.

A, Normal ganglion cells surrounded by nerve fibers; B, degenerated ganglion cells; C, granular masses at place of ganglion cells; D, small cavity containing fluid.

and may be widely distributed in the anterior horn. The smaller vessels are surrounded by a collar of lymphocytes usually lying in the perivascular lymph-spaces and spreading out, when the lesion is extensive, into the surrounding nerve tissue (Fig. 803). The arteries show less of this perivascular infiltration. Collections of round cells, also, may be demonstrated in the brain or cord, are sometimes found in groups surrounding and invading as phagocytes the damaged ganglion cells, and, after

destruction of the latter, may remain in the tissues as areas of infiltration (Fig. 804). These groups of neuronophages are found also in experimental poliomyelitis in monkeys. The ganglion cells, especially those of the anterior horn of the spinal cord, show a variety of changes depending upon the stage of the disease. The cell body is found early to be swollen, with disintegration of the Nissl granules. The nucleus may remain normal in position and appearance, but when extensive destruction occurs it is altered into a mass of chromatin and occasionally undergoes karyolytic destruction. The intracellular neurofibrils also atrophy. While these cell changes are most marked in the spinal cord, and are often limited to a certain region of that organ, moderate lesions are usually present, in addition, in all cases in the brain and medulla. So, too, the perivascular exudate is often present in the brain in cases not giving cerebral symptoms. On the other hand, the lesion may be that of an acute encephalitis, with changes more extensive and more marked than those usually seen in the spinal cord. As the process becomes chronic, phagocytosis of the ganglion cells is completed, the perivascular infiltration diminishes, and secondary hyperplasia of the neuroglia and of connective tissue begins (Fig. 805). The extent of the changes naturally depends upon the amount of the destruction in the acute stage. Many ganglion cells may escape permanent damage, but there may be no normal ganglion cells present in the anterior horns of considerable areas of the spinal cord if the lesion has been extensive. Atrophy of the anterior roots, the intraspinal tracts, and the muscles supplied from the diseased area is regularly found. Occasionally degenerations are seen in the anterolateral and cerebellar tracts and the posterior columns of the cord.

Acute Ascending Paralysis—Landry's Paralysis.—This is a rare disease characterized clinically by a rapidly ascending paralysis, beginning in the lower extremities and progressing upward to involve the body, arms, and head.[1] Recently a number of cases have been reported in which the lesion was an acute myelitis with or without an accompanying polyneuritis, and congestion, hemorrhages, and circumvascular infiltration (Fig. 806), the ganglion cells being in various stages of degeneration.[2] Lesions occasionally seen in other organs consist of acute splenic enlargement, swelling of the mesenteric nodes, and infarcts in the intestine and lung. A great variety of parasites have been isolated from the lesions, including streptococcus, anthrax and tubercle bacilli, and an organism of the Friedländer type. In many instances the disease is evidently an acute infectious myelitis with various inciting agents. That the organism may

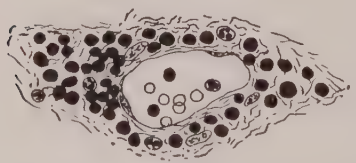


Fig. 806.—Landry's Paralysis.

Showing acute inflammatory process about blood-vessels, with leucocytes in the walls.

[1] For an excellent description of the condition in soldiers during the World War, see *Casamajor, L.*, Acute ascending paralysis among troops, Arch. Neurol. and Psychiat., 1919, ii, 605.

[2] For further details, see *Bailey* and *Ewing*, New York Med. Jour., 1896, lxiv, 1; *Cramer, A.*, Centralbl. f. allg. Path., 1892, iii, 6; and *Schmaus, H.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix[1], 396.

occasionally be the same as that found in poliomyelitis is now generally believed.

Inflammation and Degeneration of the Nerves. (*Neuritis.*)

In the nerves, as in the brain and cord, degenerative changes commonly accompany inflammation, and a distinction is often difficult. The difficulty in sharp differentiation lies in the fact that degenerative changes in nerves, when intense or long continued, often lead to inflammations, and that inflammatory conditions in nerves often determine secondary degenerative changes in the nerve fibers.

Acute Exudative Neuritis.—Acute inflammation of the nerves may occur as the result of injury, or it may be secondary to an inflammatory process in their vicinity, although, owing to the dense lamellar sheaths and the special blood supply, the nerve trunks may escape participation even in very severe inflammatory processes in surrounding tissues. The inflamed nerve may be red and swollen and infiltrated with serum and pus cells. The process may undergo resolution or terminate in destruction of the nerve, or it may become chronic and result in the formation of new connective tissue. Degeneration and regeneration of the nerve fibers, similar to those described as following division of nerve trunks, may occur in acute neuritis.

Multiple Neuritis (Degeneration).—While for convenience of reference described under its usual title, this lesion is probably always a degeneration, and would be properly classified under the head of neurone degenerations of toxic origin. It is caused by the action of certain mineral poisons, for example, alcohol and lead. It occurs as a complication of, or succedaneum to, certain infectious diseases, for example, diphtheria, septicemia, measles, smallpox, etc. It is sometimes apparently idiopathic. Changes of a degenerative nature are found in the peripheral nerves, and are more marked near the peripheral than near the cord. Thus the most common nerves affected are the anterior tibial and the radial. The most marked changes are in the nerves themselves, there being little or no change in the connective tissue. More rarely, especially in very acute cases, there are reddening and swelling with some inflammatory reaction in the interstitial tissue. The fiber lesion shows best in specimens treated with osmic acid and teased in glycerin (Fig. 807). Here the myelin sheath is seen to be broken up, and instead of a continuous envelope of black-stained myelin, the myelin is represented by larger or smaller black droplets scattered along a broken or degenerated axis-cylinder. There may be some increase in the connective tissue. The sheath of Schwann is usually intact. It is of interest to note that in a number of cases (as yet too few to warrant general conclusions) changes have been found in the cells of the anterior horn analogous to those found after injury to motor nerves. The muscles supplied by the affected nerves show various stages of atrophy. The cord and meninges usually remain normal. In some cases a spinal meningitis and more or less myelitis have been described.[1]

[1] For bibl., see *Kattwinkel, W.*, and *Kerschensteiner, H.*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1903, ix[1], 1.

Chronic Interstitial Neuritis.—This is essentially a chronic interstitial inflammation resulting in an increase of the connective tissue in the nerve sheaths and intrafascicular bands. As a result of this the nerve fibers undergo atrophy from pressure, the medullary sheaths and finally

Fig. 807.—Degeneration of Nerve Fibers in Multiple Neuritis.
From a case of alcohol poisoning. Specimen stained with osmic acid. The broken-down medullary sheath and fat droplets are stained deep black.

the axis-cylinders being in many of the fibers partially or completely destroyed. The condition is most frequently seen in leprosy.

Tic Douloureux.—Changes in the peripheral branches of the fifth cranial nerve removed from cases of obstinate trifacial neuralgia have been reported in a considerable number of cases. These changes consist in degeneration of the axis-cylinders and of their medullary sheaths. In a smaller number of instances changes have been reported in Gasserian ganglia removed from such cases. The changes in the ganglia consist in atrophy and disappearance of the nerve cells with increase in the connective-tissue elements. A peculiar shrunken condition of the cell in which the cell retracts to one side of its cell space has been seen; but none of these lesions can be considered as necessarily characteristic.

Chronic Inflammation and Degeneration of the Brain and Cord.

While this term should be applied only to a primary increase in the neuroglia elements at the expense of the parenchymatous, thus making the degeneration of the nerve tissue proper entirely secondary, it is often difficult to eliminate the possibility of a primary degeneration of the nerve cells. Histologically the lesion consists in a proliferation of the neuroglia elements. The neuroglia cells increase in number, some of the new-formed cells having many processes, others few. In the early cellular stage of its formation the proliferative area is soft and gelatinous, and tends to increase the size of the part. With further progress of the sclerosis, there is a disproportionate development of fibers attached to the cells, and finally of fibers independent of cells. With the increase of fibers the affected area becomes firmer, making a sort of dense felt-work of interlacing fibrils. In this meshwork are found nerve fibers in various stages of degeneration.

Chronic Interstitial Encephalitis—Sclerosis.—This lesion of the brain tissue may occur diffusely occupying an entire lobe or more or less of the whole brain, or in circumscribed small areas. It consists essentially in an increase of the connective-tissue elements, the neuroglia, and an atrophy of the nerve elements, particularly the ganglion cells and the medullary sheaths of the nerves. With these changes are usually associated the formation of Gluge's corpuscles, corpora amylacea, granular and fatty degeneration of the nerve elements, and thickening and pro-

liferation of cells of the walls of the blood-vessels. The areas of sclerosis may be very dense and hard, or gelatinous in consistence.

The diffuse form of sclerosis is most frequently seen in general paresis of the insane, and not infrequently in the brains of drunkards.

A peculiar feature of disseminated sclerosis is that the patches, whether in the brain or cord, do not induce the expected secondary degeneration. It is, in fact, uncommon to find secondary degeneration resulting from even a large patch of sclerosis. This is believed to be due to the fact that in nearly all of the patches the axis-cylinders persist even after complete destruction of the medullary sheaths.

The circumscribed form of sclerosis, multiple sclerosis (*sclérose en plaque*), is much more common than the diffuse form, and may occur in the brain alone, or more commonly be associated with a similar lesion in the spinal cord. The areas of sclerosis vary in size from that of a pea to that of an almond. They may be few or numerous, they may be white, grayish, or grayish red in color, and are usually but not always sharply outlined by the unaltered brain tissue. Although in many cases the increase in the connective-tissue elements seems to be the primary lesion, and the degeneration of the nerve elements secondary to this, it is quite possible that in some cases the increase in connective tissue may be secondary to a degeneration of the nerve elements from loss of nutrition or from other causes.

There is reason for the belief that multiple sclerosis may sometimes be the result of disseminated local necrotic lesions of acute infectious diseases—scarlatina, for example—occurring at an early period of life.

General Diseases of Brain.

GENERAL PARESIS. (Dementia Paralytica.)

Paresis[1] is peculiarly a disease of modern times, no description of a case having been published during the eighteenth century. That it is syphilitic in its origin has long been believed; and of late years the very constant demonstration of the Wassermann complement fixation reaction either in the blood or in the spinal fluid has given additional confirmation to this opinion, while the recent demonstration of the Treponema pallidum in the cortex of persons dying of paresis has given a final decision.[2]

Nevertheless, there are other factors than syphilis which play a part in the disease. One of these is race. The great prevalence of paresis in civilized races is in contrast with the practical absence of the disease among the negroes of Africa, in whom syphilis is a common occurrence.

[1] The best monograph on paresis is that of *Kraepelin, E.*, translated by Moore as Nervous and Mental Disease Monograph Series No. 14, New York, 1913.

For histological details see *Nissl* and *Alzheimer*, Histologische u. histopathologische Arbeiten, Jena, 1904, i, 1; also *Spielmeyer, W.*, Lewandowsky, Handb. d. Neurol., 1912, iii, 488; and *MacIntosh* and *Fildes*, Brain, 1914, xxxvii, 178. See also, *Mott, F. W.*, Nature of the condition termed parasyphilis, Arch. Neurol. and Psychiat., 1914, vi, 1; *Sands, I. J.*, General paralysis, Neurol. Bull., 1921, iii, 72.

[2] *Noguchi, H.*, and *Moore, J. W.*, Demonstration of T. pallidum in brain in general paralysis, Jour. Exper. Med., 1913, xvii, 232; *Noguchi, H.*, New technique for staining T. pallidum, Jour. Am. Med. Assn., 1921, lxxvii, 2052; *Stevenson, G. S.*, Staining spirochetes in nervous tissue, Arch. Neurol. and Psychiat., 1922, vii, 349.

Nevertheless, when the negro adopts civilized life, he becomes even more susceptible to paresis than his white co-inhabitant of large cities. It seems very probable that alcohol to excess, mental strain, and heredity are important factors in the etiology of paresis, even though syphilis may have the decisive rôle, for of those having the latter disease only a very small proportion ever develop paretic symptoms. The symptoms begin, as a rule, long after the infection; rarely do they appear within five years of the appearance of the chancre. In juvenile forms, the infection is congenital. The sex ratio was originally preponderantly masculine, even as high as eight to one; now the proportion is three times as many males as females.

There is considerable evidence of recent date pointing to the fact that different strains of the specific organism may exist, and that certain groups of Treponema pallidum may have a special affinity for the nervous system, while other varieties attack the bone or skin by preference; but a final decision has not yet been reached on this point. The Wassermann reaction is present in the blood or in the spinal fluid; and the latter also contains an increased number of lymphocytes and excessive quantities of globulin, and gives a characteristic reaction when mixed in suitable quantities with a colloidal suspension of gold, which in many instances differentiates the disease from purely syphilitic conditions with similar symptomatology.[1]

The tissue lesions are many and complex. There are two simultaneous and independent processes in the brain; one, the destruction of the nervous tissue, and the other the disease of the vessel walls with its consequences.

Macroscopically, no characteristic lesion exists. The dura is often adherent to the calvarium; pachymeningitis interna hemorrhagica or hematoma of the dura is not infrequent; and there may be also more or less widespread fresh superficial hemorrhages. The pia is almost always cloudy and thickened, the thickening being especially evident along the vessels. These alterations of the pia are usually most apparent over the anterior and middle portions of the frontal lobes, and in late cases also the removal of the pia is often impossible without laceration of the brain substance. The posterior portions of the brain rarely show these changes. The Pacchionian bodies are frequently much enlarged; and the brain in late cases is almost always atrophic; the convolutions are shrunken, especially in the anterior two thirds of the brain; and not infrequently there are also found irregular depressions, over which the membrane may be stretched, with a collection of serum beneath. Occasionally, the whole cortex shows a diffuse shrinkage. The ventricles are usually dilated, and the ependyma shows more numerous and prominent granules than normal. The cortical atrophy is expressed in a great reduction in the weight of the brain, which amounts on the average to 100 to 150 grams. It must, however, be remembered that similar changes, though often less extensive, may be seen in senile arteriosclerotic processes, and in cases of chronic alcoholism accompanied by a chronic leptomeningitis.

[1] For a discussion of the nature and interpretation of the colloidal gold reaction, see references on pages 318 and 1202.

Extensive and characteristic syphilitic lesions are not extremely frequent in the other organs of the body; syphilitic aortitis is, however, frequent in paretics, though aneurysm is rare.

Microscopically, the changes in the brain in paresis are fairly characteristic, and consist in general of a diffuse inflammatory process with degenerative phenomena in the functional portions of the nervous system, and more or less extensive changes in the glial material. The inflammatory processes consist chiefly of a diffuse infiltration of the meninges and the adventitial lymph-spaces with plasma cells and lymphocytes. This infiltration is most extensive in the cerebrum, but is almost always present to a limited extent in the cerebellum, central portions of the brain, and the spinal cord. In the cerebrum the cortex is the portion which is especially attacked by the inflammatory processes. The collection of plasma cells in the lymph-sheaths of the more delicate cortical vessels is quite characteristic of paresis and is constantly present. Nevertheless similar perivascular lesions, either lymphocytic or plasma cell, are also seen in syphilitic meningoencephalitis, in carcinomatous and tuberculous lesions, in sleeping sickness, cerebral types of poliomyelitis, and rabies. The paretic lesion is, however, more diffuse and constant. The plasma cells are far more abundant than the lymphocytes. Occasionally, mast cells with coarse granules and large phagocytic cells filled with fatty material and pigment are seen. The cortex may be involved in cases in which the pia is relatively free from inflammatory lesion. The perivascular adventitial connective tissue may also proliferate and extend out into the glia, penetrating the neighboring gray substance in the form of long, rod or sausage shaped cells with long, delicate projections. Some of these types of cells are, however, unquestionably glial in nature. Endothelial hyperplasia may lead to extensive new formation of capillaries. In sections the vessels seem very numerous as compared with a normal brain; but this is partly due to the shrinkage of the brain tissue causing an apparent increase.

The most striking lesion of the functional nervous tissue is the disappearance of the medullated cortical fibers with atrophy of the supraradial reticulum and the tangential fibers in addition, though these lesions are not characteristic of paresis, nor indeed are they constant even in fairly well marked cases. Another peculiar appearance is produced by the local disappearance of the medullated fibers in the cortex, leaving small oval or band-like areas in which no medullary material can be made out, even with suitable stain. The axis-cylinders may be retained under these circumstances. A similar lesion is seen, however, in multiple sclerosis. This local destruction of the cortical medullary tissue of the brain may attack only a few convolutions, but as the lesion progresses the axis-cylinders disappear, as do also the ganglion cells.

Glial hyperplasia takes place on the free border of the cortex, while the tissue below may not show an excess of fibers. As the process becomes more extensive, a thick network of fibers may grow down into the substance of the brain, and also grow out in the form of brush-like processes towards the pia, thus forming adhesions between this membrane

and the cortex. The same hyperplasia of the glia may be found about the blood-vessels especially in the deeper layers. The glial overgrowth is not directly connected with or proportional to the destruction of the nerve cells of the cortex, but the nerve tissue itself seems to be directly damaged by the poison of the syphilitic organism. After this has occurred, the pia may undergo extensive hyperplasia, but occasionally such an overgrowth may not occur. These extensively hyperplastic changes in the glia cells are especially characteristic of the slowly progressive stages of the disease. In paresis with a more rapid course, the glia cells more often assume what may be described as the ameboid form and apparently act as phagocytic cells in the removal of the fragments of the degenerating cortical nerve cells.[1] With the continuation of the process to the cortical cells, all sorts of degenerative processes occur in the bodies of the ganglion cells themselves, which are well demonstrated by the Nissl and Bielschowsky stains. Disappearance of the chromatic granules, destruction of the nucleus, vacuolar degeneration, atrophy, and pigmentation are the most evident changes. This destruction may go on to the complete removal of all trace of ganglion cells; it often extends only to a particular group; the second cellular layer not infrequently remains fairly unaltered in the earlier stages, and even when the disease is extensive the process is sclerotic rather than one leading to the complete destruction of the cells themselves. On the other hand, the process may be limited to particular areas, and all the ganglion cells of a small portion of the brain may be completely destroyed, so that not only the upper and middle layers, but even the deeper layers of the cortex with the large pyramidal cells may be completely atrophied. This destruction of the large pyramidal cells explains the degenerative changes in the pyramidal tract which are found in the cord in cases of this type.

While in general the lesions of paresis are most constant and best marked in the cortical regions, the remainder of the brain rarely escapes some change. The cerebellum and the spinal cord, especially the latter, show infiltrative and degenerative changes. Alterations in the ganglion cells and destruction of the nuclei for the optic muscles explain the defects of motility of the eye. In the optic thalamus and the cerebellum the degenerative process is chiefly recognizable in the proliferation of the neuroglia. In individual cases the process may be especially well developed in the cerebellum, and in the later stages of the disease, extensive degeneration in the posterior and lateral column of the cord are usually met with. In distinction to tabes, the ventral area of Hoche's bundle are frequently affected, while the posterior root zones are not so markedly altered as in tabes. The lesions of tabes, however, may coexist with those of paresis.

While the symptoms of sleeping sickness are in many ways different from those of paresis, there is a striking similarity in the lesions of the nervous system in the two diseases.[2]

[1] For a study of these granular cells, see *Schmaus*, Lubarsch-Ostertag, Ergebn. d. allg. Path., 1904, x[1], 350.

[2] See *Spielmeyer, W.*, Die Trypanosomen-Krankheiten, Jena, 1908; also in Lewandowsky, Handb. d. Neurol., 1912, iii, 538.

SENILE DEMENTIA.

The most constant gross lesion of senile dementia is a diminution in the size of the brain, often accompanied by external hydrocephalus. The convolutions are shrunken, and the furrows larger than normal, especially in the frontal portions. The pia is usually thickened, and the Pacchionian bodies are prominent. The ventricles may be enlarged and contain fluid. The larger vessels, especially those at the base of the brain, may show some atherosclerotic changes, but are more frequently normal.

Microscopically, the thickened pia shows an increase in the fibroblasts, lymphoid infiltrations, and fatty and pigmented phagocytes, and the vessels are usually thickened. The ganglion cells are extensively pigmented with a bright yellow, granular material which stains with Sudan

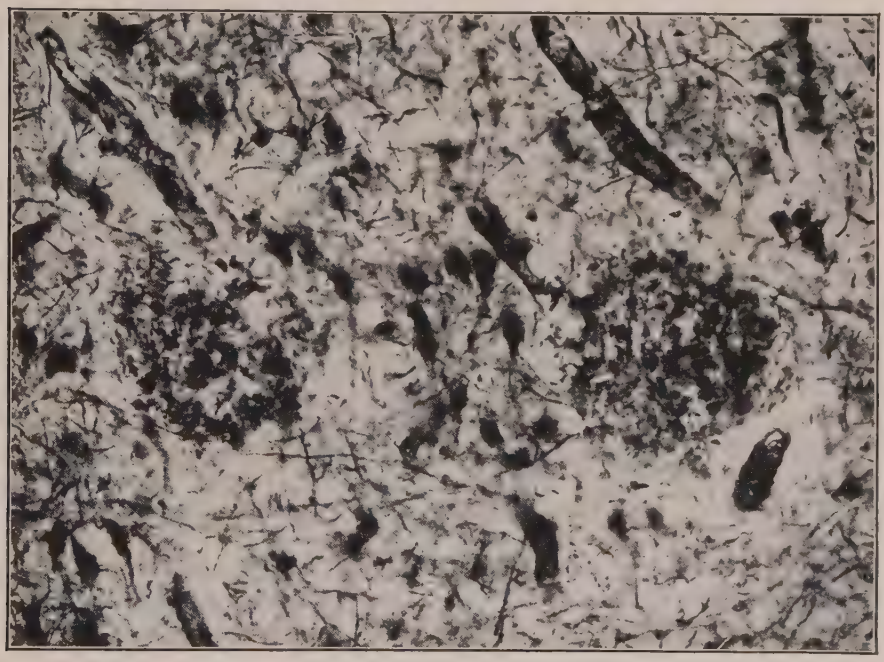


FIG. 808.—Senile plaques Bielchowsky technique. The preparation is one made by Dr. T. J. Sands.

III and blackens with osmic acid. The cell fibrils are pushed to the periphery by the pigment accumulation, and the Nissl granules also are displaced by the pigment. Similar changes in the ganglion cells are present, but less extensively, in extreme old age, in various intoxications, especially alcoholic, in paresis, and in atherosclerotic brains. In advanced cases of senile dementia, the fibrils are often greatly thickened and form a basket-like network about the ganglion cells. The pyramidal cells often show large granules in the cytoplasm which do not stain with Sudan III, but take a basic stain. Throughout the brain there is exten-

sive loss of the ganglion cells; and accompanying this atrophy of the ganglion cells there is an atrophy of the nerve sheaths and axis-cylinders of the cortical layers. The glia is increased in amount especially on the surface of the brain. Many astrocytes and small glia cells with pycnotic nuclei appear in the cortical substance. The vessels show, aside from occasional atherosclerotic changes, alterations in the endothelium, fatty infiltration and atrophy of the muscular layers, and an increase in the adventitial connective tissue. A few lymphocytes and degeneration products may collect in the perivascular lymph-spaces, but there are no extensive collections such as are characteristic of paresis.

The most characteristic morphological change in senile dementia is the appearance in the cortex of the "senile plaques," which are most satisfactorily demonstrated by the Bielchowsky stain. While these occur occasionally in the brain in old age, in dementia præcox, and in severe general diseases, they are never so abundant as in senile dementia. The plaques are formed of a feltwork of fibers composed of axis-cylinders and nerve and glia fibrils, surrounding areas in which the products of destruction of the nerve tissue have collected. The axis-cylinders frequently show buds or loops in their continuity. Ganglion cells are rarely found in the center of the plaques; occasionally a capillary occupies this position. Glia cells are found among the fibers of the plaque and about its periphery.

While the cornu Ammonis is most frequently and most extensively involved in senile dementia, similar alterations may be found in the cerebellum, the central ganglia, and the pons. Even the cord may show atrophy of fibers, growth of glia tissue, fatty and degenerative changes in the ganglion cells, and occasionally circumscribed areas of degeneration; but such changes as a rule are scanty and infrequent. A presenile type of dementia with lesions similar to those of the senile group has been described by Alzheimer as occurring in persons not over forty years of age.[1]

It should be remembered that all of the lesions of senile dementia enumerated above are merely an exaggeration of what may be called physiological senile alterations occurring in a moderate degree in the cerebrospinal system of the very aged.[2]

PARALYSIS AGITANS.

This is a chronic, usually progressive disease, characterized by muscular rigidity, weakness, tremor, and a peculiar attitude of the patient. The disease occurs in men twice as frequently as in women, and not infrequently there is a history of heredity. The present view of pathologists is that the disease is due to an atrophy of the large motor cells of the corpus striatum with some secondary thinning of the striohypothal-

[1] *Lambert, C. I.*, Clinical and anatomical features of Alzheimer's disease, Psychiat. Bull., 1916, i, 413; *Sands, I. J.*, Senile and presenile psychoses, Neurol. Bull., 1918, i, 377.

[2] The most valuable monograph, with bibliography, on the histological changes in the brain in senile dementia, is that of *Simchowicz, T.*, Nissl and Alzheimer, Histologische und Histopathologische Arbeiten, Jena, 1911, iv, 267. See also *Léri*, Le cerveau sénile, Lille, 1906; *McGaffin, C. G.*, Am. Jour. of Insanity, 1910, lxvi, 649; *Southard, E. E.*, ibid., p. 673; and *Tiffany, W. J.*, ibid., 1914, lxx.

amic radiation, the ansa lenticularis, and the ansa peduncularis. The small ganglion cells of the caudate nucleus and the putamen are not affected. There is also considerable increase in the amount of glia tissue in the affected region.

The fibers of the globus pallidus show atrophy, but no more than may be seen in cases of senile dementia. The atrophy of the loops of the nucleus caudatus is considerable, and is seen in many cases. The red nucleus and the pontine ganglia are not diseased. Numerous small hemorrhages have been found in the optic thalami. Changes in Nissl's granules and the ganglia cells of the cortex, cerebellum, and spinal cord are frequent; but none can be considered as characteristic of paralysis agitans. Vascular degenerations of the arteriosclerotic type are often present, but are due solely to conditions not connected with the disease. Paralysis agitans may, therefore, be considered as due to destruction of the large ganglion cells of the corpus striatum. This results in motor disturbances due to loss of control of the automatic and association activities of the muscles through the connections with the nuclei of the hippocampal regions and the extrapyramidal tracts of the spinal cord. As this mechanism is infracortical, its activities are unconscious, but as it is under the control of the higher cortical centers the tremor may disappear on voluntary motion.[1]

A great many other changes in the central nervous system have been described, but these are probably unessential and due merely to the accompanying senile and arteriosclerotic processes which occur in many persons of advanced years. Among these are extreme fatty degeneration of the ganglion cells, especially in the anterior horns of the cervical and lumbar cord, the presence of large numbers of corpora amylacea, which have been described by a number of observers in the posterior columns of the cord, as well as the obliteration of the central canal, none of which are characteristic of this disease. When the larynx is affected by the tremor, degenerative changes have been found in the vagoglossopharyngeal nucleus.[2]

While a few examples follow trauma, the frequent occurrence of the Parkinsonian syndrome coincident with the recent world-wide epidemic of encephalitis lethargica has called attention to the important rôle which this infection plays in the production of a special type of paralysis agitans. Unquestionably many of the cases occurring in young adults not heretofore understood are due to a mild encephalitis which, occurring several years before, has passed unnoticed. The first investigation of these cases suggested that the pathological condition is due to a selective atrophy of the motor cells of the pallidal system.[3] Subsequent studies showed that the lesion was situated chiefly in the substantia nigra and the changes in the globus pallidus were considered secondary to those of

[1] *Hunt, J. R.*, Brain, 1917, xl, 58; Neurol. Bull., 1918, i, 237; and Arch. Int. Med., 1918, xxii, 647.

[2] *Foster, E.*, and *Lewy, F. H.*, Lewandowsky, Handbuch d. Neurologie, 1912, iii, 920 (bibl.); *Mendel*, Paralysis agitans, Berlin, 1911; *Gordinier, H. C.*, Am. Jour. Med. Sc., 1899, cxviii, 648; *Dana, C. L.*, ibid., p. 503.

[3] *Hunt, J. R.*, Arch. Int. Med., 1918, xx, 647.

this region, or merely accidental findings.[1] Further investigation has shown that the lesions are often much more extensive, involving the internal capsule, thalamus, caudate nucleus, and the frontal lobe. Under these circumstances, careful quantitative estimations of the cellular changes are important and it has been found[2] that in three cases of post-encephalitic paralysis agitans an average decrease in the number of neurons from 57 to 87 per cent. has occurred in the substantia nigra without significant lesions in the globus pallidus. In this connection it is not without interest that in patients with general paralysis definite pathological changes were found in the basal ganglia which may be responsible for the inexpressive facies and the fine tremors about the eyes and mouth occasionally seen in this disease.[3]

Some observers[4] consider the classic Parkinsonian lesion a chronic progressive degenerative condition of the entire central nervous system, a position well supported by the clinical symptoms in advanced cases, and it is not therefore proper to look on paralysis agitans merely as an end-result of encephalitis. Evidently under this general title there are numerous closely related clinical conditions associated together, of which the classic paralysis agitans is due to a degenerative type of lesion involving the extrapyramidal system, mainly the basal ganglia and especially the substantia nigra, while the lesion in the post-encephalitic syndrome, though degenerative in a degree, is also combined with inflammatory phenomena.

PROGRESSIVE LENTICULAR DEGENERATION. (Wilson's Disease.)

The characteristics of this disease[5] are an atrophic cirrhosis of the liver beginning in youth or adolescence and accompanied by degeneration in both lenticular nuclei.

The liver lesion is the usual type of atrophic cirrhosis; the spleen is also enlarged though not invariably. In those cases in which death occurs early the central nervous system may show no microscopical lesions; when, however, the disease has persisted for some time the pathological changes in the nucleus may be striking. The softening is bilateral involving especially the putamen and varies from a slight discoloration and a sponginess of the tissues to shrinkage and atrophy and, finally, complete disintegration and excavation of the ganglia. The caudate nucleus has been described as slightly shrunken but not disintegrated.

Microscopically, there is glial overgrowth which softens afterwards. There is often a great increase in the number of glial nuclei; the nerve fibers and nerve cells of the normal nucleus disappear. There is a certain amount of infiltration with phagocytic wandering cells. The blood-

[1] *Hunt, E., L.* and *Cornwall*, Jour. Am. Med. Assoc., 1925, lxxxiv, 29, and *Strauss* and *Globus*, Trans. Am. Neurol. Assn., 1923, 329.

[2] *McKinley* and *Gowan*, Arch. Neurol. and Psychiat., 1926, xv, 1.

[3] *Houlton, T. L.*, Arch. Neurol. and Psychiat., 1927, xvii, 214.

[4] *Hohman*, Pathologisch-anatomische Untersuchungen über den encephalitischen Parkinsonismus, Arb. a. d. neurol. Inst. a. d. Wiener Univ., 1925, xxvii, 1.

[5] *Tilney, F.*, Neurological Bull., 1918, i, 243; *Wilson, S. A. K.*, Lewandowsky, Handb. d. Neurol., 1914, v, 951.

vessels show no special change. The pons, medulla, cord, nerves, and muscles are also normal. Degeneration secondary to that in the lenticular nucleus has been found in the ansa lenticularis and the corpus Luysi.

The characteristic symptoms of the disease are motor disturbances; tremor is marked; spasticity or hypertonicity is also always present. Tonic cramps are a late symptom. The mouth is often held open as if the patient were laughing. Dysphagia is common, and loss of ability to speak. The dysarthria is not severe in the early states of the disease

Fig. 809.—Tuberculosis of Left Frontal Lobe.

but later in children who have learned to speak may become so great that they are not able to utter a word. This inability is due to the stiffness of the muscles of speech. In the later stages muscular weakness and emaciation develop and control over the sphincters is lost. The children are often simple-minded.

About 75 per cent. of the cases are familial, though the disease is neither congenital nor hereditary. Its cause is unknown, but syphilis and alcoholism can be excluded as factors. Similar symptoms are occasionally noted in illuminating gas poisoning when softening of the lenticular nuclei has occurred.[1]

[1] *McConnell* and *Spiller*, Jour. Am. Med. Assn., 1912, lix, 2123; and *Hill, E.*, and *Semerak, C. B.*, Jour. Am. Med. Assn., 1918, lxxi, 644.

Specific Inflammatory Lesions of the Nervous System.

TUBERCULOUS LESIONS IN THE NERVOUS SYSTEM.

Tuberculous inflammation whether of the brain or of the cord is usually secondary to tuberculous inflammation in other organs, and is most frequent as an extension of tuberculosis of the meninges. In the brain substance it usually manifests itself in the formation of circumscribed masses of new tissue from 0.5 to 1 centimeter in diameter, or larger. These may be single or multiple, are most common in young persons, and very frequently occur in the cerebellum (Fig. 810). They are apt to occur in connection with tuberculous inflammation of other organs. They are frequently solitary tubercles, each consisting of a dense central cheesy mass, around which is a grayish zone containing tubercle granula

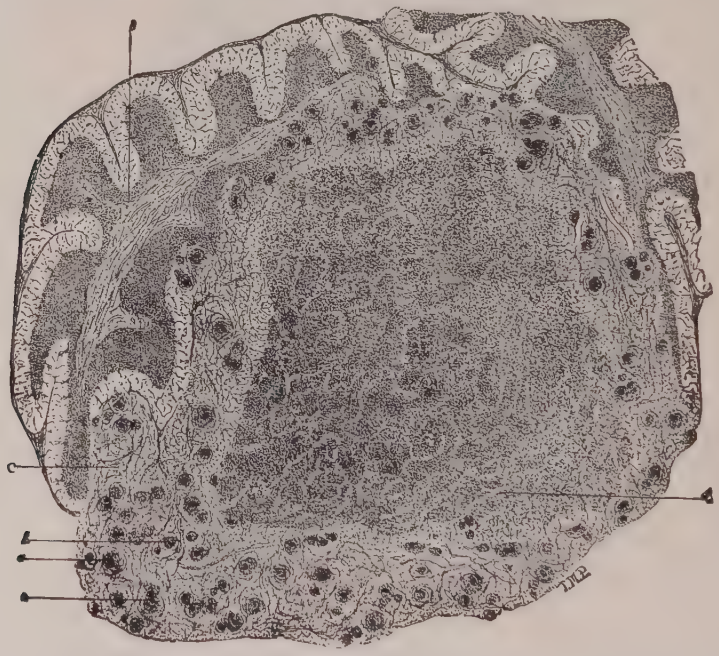


FIG. 810.—SOLITARY TUBERCLE OF CEREBELLUM.
a, *a*, Miliary tubercles with giant cells; *b*, *b*, miliary tubercles without giant cells; *c*, diffuse tubercle tissue; *d*, central cheesy mass; *e*, nerve tissue of the cerebellum.

and numerous small spheroidal cells, with occasionally larger polyhedral cells and giant cells. They do not, as a rule, seem to be formed by an aggregation of miliary tubercles, although these may be present at the periphery. They sometimes suppurate and break down, and then they simulate simple abscesses. Tubercle bacilli have been found in these solitary tubercles.

Conglomerate and scattered miliary tubercles of the ordinary form sometimes occur in the brain, usually in connection with tuberculous inflammation of the meninges or ependyma. The lesion is not infre-

quently overlooked, appearing as minute tubercles which often occur on the lateral aspect of the septum pellucidum and the terminal striae of the anterior, posterior and inferior horns and the lateral extensions of the fourth ventricle. Such miliary tubercles are often arranged along the blood vessels and contain numerous organisms. A moderate number of lymphocytes and polynuclears may be present occasionally in such quantities as to resemble abscesses. This form originates as a hematogenous infection. The solitary tubercles are often secondary to a tuberculosis of the middle ear or mastoid, or to an extension from tuberculous lesions of the cervical and bronchial nodes, the lungs, the bones, intestine, prostate or testicle. If the infection involves the meninges the clinical picture and the terminal result is due to the tuberculous meningitis which follows, but it may remain localized and then give rise to symptoms of brain tumor accompanied by epileptiform attacks and monoplegia but rarely causes increased cerebral pressure and therefore choked disc is infrequent.

Another and much rarer type of lesion of the brain is a flat, thick, tumor-like layer of tuberculous tissue covering the convolutions and often of considerable size. Sometimes there are more than one of these plaques. The patients often have the Jacksonian type of epilepsy, with headache and vomiting, and are all supposed to be examples of cerebral tumors. The fever which is almost constantly present is the best guide to a differential diagnosis. Sections through such a tuberculous plaque show a hyaline, fibrous reticulum, usually containing large numbers of tubercles. These vary in character and age in the same specimen. The tuberculous granulation tissue is almost entirely limited to the meninges, and the cortical substance may show little but infiltration with lymphocytes and plasma cells. Sometimes, however, there is no line of demarcation and the cortex may be extensively invaded.[1] (Fig. 809.)

In the spinal cord solitary nodules may determine extensive secondary degenerations. Multiple tuberculous foci may occur in the cord. They are rare and usually secondary to tuberculosis of the spinal meninges.

Tuberculous inflammation of nerves is rare except at their origins, where it is due to an extension from tuberculous meninges. When a nerve traverses tuberculous tissues, it may be involved in the inflammatory process.

SYPHILITIC LESIONS OF THE NERVOUS SYSTEM.[2]

The virus of syphilis may affect the nervous system in two fashions; either it may attack the functional epithelium and cause the death of the ganglion cells and a growth of glia tissue accompanied by secondary degeneration in the ganglia and fiber tracts of the cord, as in tabes and general paresis; or it may attack the connective tissue and vascular portions of the brain, forming a series of products with which we are

[1] *Pardee* and *Knox*, Arch. Neurol. and Psychiat., 1927, xvii, 231 (bibl.).

[2] *Dunlap, C. B.*, Anatomical borderline between so-called syphilitic and metasyphilitic disorders in brain and spinal cord, Amer. Jour. Insanity, 1912–13, lxix, 1045. Two important reference books on syphilis of the nervous system are, *Krause, K.*, Beiträge zur Pathologischen Anatomie der Hirnsyphilis, Jena, 1915; and *Gennerich, W.*, Die Syphilis des Zentralnervensystems, Berlin, 1921.

familiar in syphilis of other organs, in other words, gummata and syphilitic granulation tissue. The vascular lesions are similar to those seen in other portions of the body. They consist primarily of a swelling of the endothelium of the vessels, with the production in the adventitia, the media, and the intimal layers of the vessels of new tissue composed of spindle cells and loose interstitial connective tissue. In this interstitial tissue, there are frequently large numbers of lymphocytes or plasma cells, and around the periphery of the smaller vessels are collections of lymphocytes and occasional plasma cells. As the process continues, the

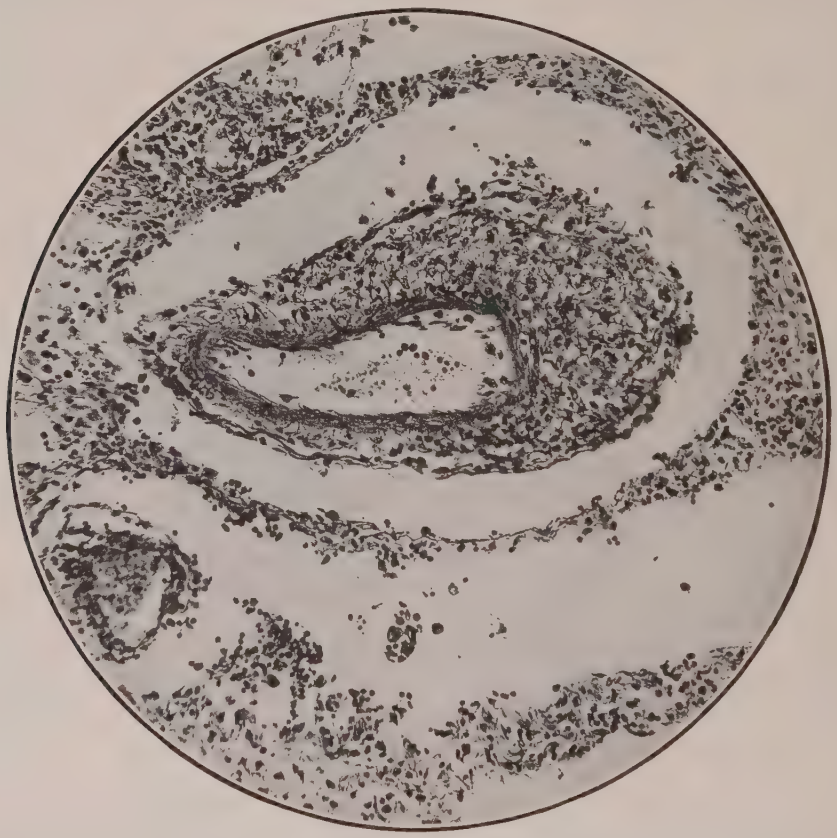


FIG. 811.—Small pial capillary from a case of cerebral syphilis, showing the thickening of the vascular wall and the perivascular exudate. The tissue was very gelatinous so that there is considerable shrinkage.

newly formed tissue gradually alters into a dense sclerotic fibrous tissue, which ultimately destroys the muscular and the elastic laminæ of the vessels. Occasionally, the process is frankly gummatous in nature, with the formation of patches of new connective tissue which break down and form necrotic masses, about the periphery of which there may be a few giant cells. The lumen of the vessel is greatly reduced in all cases, and occasionally may be entirely obliterated. While the process is most

marked in the larger vessels, it may involve also the veins and the capillaries. In distinction to general paresis, the infiltrate about the capillaries is composed chiefly of lymphocytes rather than plasma cells as in the latter disease. While the perivascular lymph-spaces do not, as a rule, contain cells from the exudate these may be present; but when the disease is extensive and long-continued, the tissue outside of the perivascular lymph-spaces is infiltrated, and under these circumstances the glia also undergoes hyperplasia. Ultimately the changes in the vessels lead to degenerative processes due to the lack of nutrition of the brain-substance supplied, thus complicating the picture. The ordinary non-specific type of arteriosclerosis may also occur in the vessels in the brains of those suffering from syphilis, but has nothing to do necessarily with the purely leutic process. Small aneurysms may form along the course of the larger vessels in both types of disease, the syphilitic and the arteriosclerotic.

The second type of syphilitic disease of the brain is the gummatous. In this, solitary or multiple gummata are formed, which arise solely in the elements of the connective tissue; the brain itself is only secondarily involved. The gumma is formed of a peripheral mass of granulation tissue containing a great variety of cells of the epithelioid variety, with lymphocytes, plasma cells, and occasionally mast cells. The plasma cells are usually about the vessels. In the interior of the mass there is usually an area of cheesy degeneration, about the periphery of which may be found a few giant cells. The gumma, if it is small, may ultimately be replaced by dense connective tissue, and leave little else than a scar in the brain substance. The larger gummata may soften in the center and ultimately become calcified. The cells of the nervous system are involved secondarily; the glia especially undergoes active hypertrophy and many types of glial cells, including the ameboid variety, may be observed. Such cells may contain pigment and even become calcified. Ganglion cells in the immediate neighborhood of the gumma are frequently degenerated and stain poorly, and their processes appear very sharply demarcated against the edematous brain tissue. The nerve fibers also suffer. The medullary sheath may be swollen and the fibers broken up, and over small areas completely disappear. Such changes, however, are limited to the region of the gumma and do not involve the entire brain substance, as do the changes in paresis.

The most frequent form of cerebral syphilis is a diffuse, basal, gummatous meningitis, beginning in the subarachnoid tissue of the region of the chiasm and spreading from this point more or less over the entire base of the brain. The newly formed tissue is usually soft and gelatinous with areas containing firm connective-tissue strands attached to the basal portion of the brain. The gummatous material penetrates the depressions in the brain substance and covers the region of the cranial nerves. The optic nerve and the third nerve especially are frequently diseased, which explains the fact that in 40 per cent. of cases of cerebral syphilis there are changes in the eye grounds. Hemorrhage and softening are not infrequent in the gummatous material. Syphilitic meningitis of the

convexity occurs, but is less frequent. With these lesions go constant changes in the cerebrospinal fluid. The Wassermann reaction is regularly positive, the amount of globulin is increased, the cells are usually far above the normal, and the alterations in colloidal gold solutions produced by the addition of a measured quantity of the spinal fluid are quite constant.[1]

Syphilitic inflammation in the spinal cord is usually secondary to a similar process in the spinal meninges. Gummata, when they occur, are modified in size and shape by the anatomical restrictions of the vertebral canal. Such masses are significant chiefly because of the more or less extensive secondary degenerations which they induce.

Syphilitic lesions of the nervous system may occur in either the inherited or the acquired type of the disease. In the former, they usually show changes early in life, though cases have been reported after puberty. More commonly, cerebral syphilis is a manifestation of the acquired disease, occurring from ten to twenty years after the initial lesion; but cerebral symptoms may make their appearance within a few months after the chancre. Extensive gummatous formation in the brain is rare; many of the cases giving clinical symptoms show a relatively slow growing vascular or perivascular lesion with very moderate meningeal inflammation.

ACTINOMYCOSIS.

Actinomycosis of the brain has been described. It is a rare form of brain infection, and is usually secondary to actinomycosis of the neck or face. The condition is apt to lead to suppuration and abscess formation. A case has been reported in which the disease was apparently primary in the brain.[2]

LEPROUS INFLAMMATION.

This occurs in the peripheral nerves and consists in the formation within the nerves of masses of new-formed tissue somewhat resembling granulation tissue. In the cells of this tissue multitudes of characteristic bacilli are uniformly found (see page 308). The injuries to the nerve fibers explain the clinical symptoms of the variety of leprosy known as lepra anæsthetica.

TUMORS.

Tumors occurring in the nervous system may be of the types found in the other organs or of types peculiar to nervous tissue. They may be primary, or secondary to similar growths in other parts of the body.

Tumors of the Brain.[3]

Myxoma, fibroma, lipoma, and **osteoma** are rare forms of brain tumor.

[1] For a study of the comparative value of various tests, see *Hammes, E. M.*, Am. Jour. Med. Sc., 1917, cliv, 625. See, also, *Vogel, K. M.*, Arch. Int. Med., 1918, xxii, 496; and *Solomon, H. C.*, Non-concomitance of spinal fluid tests, Arch. Neurol. and Psychiat., 1920, iii, 49.

[2] For further details, see *Howard, W. T.*, Jour. Med. Research, 1903, N. S. iv, 301.

[3] For the subject of brain tumors, with bibl., see *Oppenheim*, Die Geschwülste des Gehirns, 2d ed., Vienna, 1902; and *Bruns*, Die Geschwülste des Nervensystems, 2d ed., Berlin, 1908.

Neuroglioma Ganglionare.—This is a form of tumor probably due to disturbances in the development of the brain. It is peculiar to nervous tissue and occurs in the form of circumscribed tumors or of diffuse enlargements of portions of the brain. The pia mater over these tumors is unchanged and the convolutions retain their shape. The tumors are formed of neuroglia, with many astrocytes in which are contained little groups of ganglion cells.

Glioma.—This is the most common tumor of the brain, and like the preceding is found only in the nervous system or in areas where nerve material exists during embryonic life, for example, at the root of the nose, and over the sacrum, the anterior and posterior terminations of the neural canal. It occurs with special frequency in children and young adults. Such tumors occur in all parts of the brain, but are found most frequently in the cerebrum. There may be a single tumor, or there may be several such tumors in different parts of the brain; some of them attain a large size, even more than one-half of a hemisphere may be involved. These tumors may be sharply circumscribed or may merge imperceptibly into the brain substance. They may be white and hard; gray, soft, and gelatinous; infiltrated with small hemorrhages; or partly degenerated and softened. The center of a glioma may break down and become soft and necrotic or even fluid, and in this way a cyst may be formed having a wall of gliomatous tissue. The brain tissue around the tumors may be inflamed or necrotic. The tumors arise from the neuroglia, and are composed of neuroglia cells and their delicate interlacing processes; the relative quantity of cells and fibrils varies in different tumors. If the tissue is of a loose formation with wide meshes between the fibers it presents a myxomatous appearance, and has been described as a *myxoglioma*. When the cellular elements are very numerous the tumor is often referred to as a *gliosarcoma*. This term should, however, be reserved for tumors in which both connective tissue and glial elements are present, in other words, for a mixture of a glioma and a sarcoma. Such tumors occur very rarely. The very cellular gliomata, especially those containing large multinucleated cells, should be called *spongioblastomata* rather than gliosarcomata, the spongioblasts being the embryonic ancestors of the glial cells. These spongioblastomata are somewhat less frequent than the astrocytic gliomata and are of rather more rapid growth, but they do not form metastases and have in general the characters of all glial tumors, a tendency to softening and to central hemorrhage being well marked.[1]

Primary sarcoma occurs in any part of the brain, and is derived from the connective tissues of the membranes, or that accompanying the blood-vessels. The tumor may be single or multiple. It is composed usually of round or fusiform cells with more or less basement substance.

Endothelioma is found in the substance of the brain. The tumors are of the types described as occurring in the pia mater.

[1] For further details see, Tumors of the Glioma Group, *Bailey* and *Cushing*, Philadelphia, 1926.

Cholesteatoma occurs chiefly in connection with the pia, but the tumors may project into the substance of the brain and cause symptoms. These tumors are very slow growing and usually originate in deposits of squamous epithelial cells left during the closure of the neural groove. Grossly the tumors are irregularly spherical, and very hard, and when cut across are pearly white and rather loose in structure. Microscopically they are composed of flattened epithelial cells mixed in various proportions with cholesterin crystals. It is sometimes difficult to demonstrate the epithelial origin of these growths and the cholesterin crystals may lie in a mass of granulation or firm connective tissue, often inclosed in for-

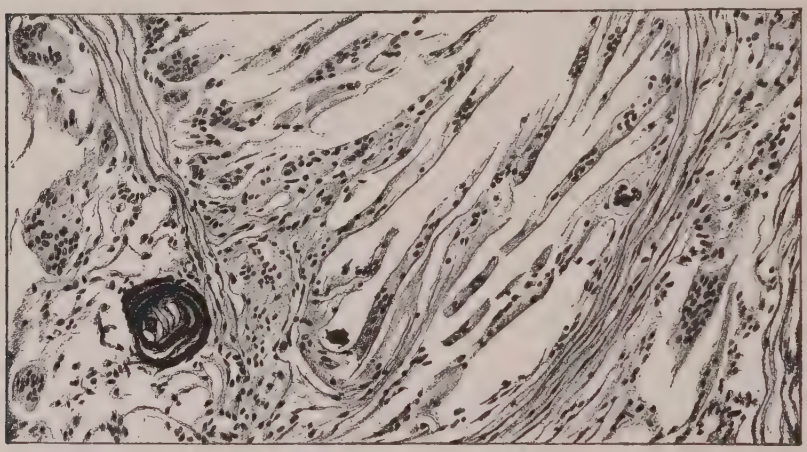


Fig. 812.—Cholesteatoma of Brain.

eign body giant cells (Fig. 812). There is a possibility that a few of these tumors do not originate primarily in epithelial remnants; but this question is not yet finally decided.[1]

Angioma occurs in the substance of the brain, and, like the nævi of the skin appears to be congenital.

Chorionepithelioma of the uterus metastasizes frequently into the brain and forms considerable masses, usually very hemorrhagic. Indeed, the symptoms of hemorrhage may completely mask those due to the tumor, and the sudden death of the patient may be ascribed to apoplexy.

Carcinoma occurs in the brain, but is almost always secondary to carcinoma in some other organ. Owing to the greater blood supply to the left hemisphere, the metastases are much more frequent on the left than on the right side of the brain.[2]

[1] For a study of cholesteatoma of the brain, see *Thomas, J. J.*, Jour. Med. Research, 1901, N. S. i, 220 (bibl.). See also *Ribbert*, Geschwülstlehre, 2d ed., Bonn, 1914, p. 486 (bibl.).

[2] For an interesting statistical study of metastasis in the central nervous system, see *Krasting, K.*, Ztschr. f. Krebsforsch., 1906, iv, 315 (bibl.).

Tumors of the Cord.

In the pia mater of the cord are sometimes found small **fibromata, osteomata,** and **lipomata.** Multiple fibromata occasionally occur in the cord in connection with multiple fibromata of the peripheral nerves.

Endotheliomata of the types described as existing in the pia mater of the brain are much more rarely found in the pia mater of the cord.

A fatty **sarcoma** of the pia mater, which infiltrated the cord, formed a tumor as large as a filbert, and had for twelve years caused gradually increasing paraplegia, has been described.[1]

Two curious cases[2] of diffuse sarcoma and one of endothelioma of the pia mater of the whole length of the cord are recorded. In each case the pia mater of the whole length of the cord was diffusely thickened and studded with nodules. In two of the cases the growth was composed of round cells, in the third case of large endothelial cells arranged in alveoli. In two of the cases the clinical symptoms lasted only for about three weeks, in the third case for five months. The acuteness of the symptoms was such as to indicate the existence of spinal meningitis.

In the spinal cord itself **gliomata, lipomata, fibromata, sarcomata,** and **angiosarcomata** occur, but are rare.

When gliomata do occur in the spinal cord, the new growth is apt to extend for some distance lengthwise in the cord and to be attended with the formation of a cavity; this condition is usually described under the name of *syringomyelia.* (See p. 1177.)

Fig. 813.—Syringomyelia.
An irregular cavity in the gray matter of the spinal cord, lined by a thick layer of gliomatous tissue.

Tumors of Nerves.

The tumors of the nerves may be divided into those consisting largely of or containing new-formed nerve tissue, **true neuromata,** and the so-called **false neuromata,** which are for the most part fibromata (Fig. 221), fibrolipomata or myxomata originating in the connective tissue of the nerve (see Neuroma, page 426). **Myxosarcomata** are less common,

[1] *Turner*, Trans. London Path. Soc., 1888, xxxix, 25.
[2] *Coupland* and *Pasteur*, Trans. London Path. Soc., 1887, xxxviii, 26.

and primary **sarcomata** rare (Fig. 814). The nerves may be secondarily involved in sarcomata, or in carcinomata through which they pass, though

FIG. 814.—NEUROFIBROSARCOMA OF MUSCULOSPIRAL NERVE.

not infrequently nerves pass through these tumors without being in the least affected.

HOLES AND CYSTS IN THE BRAIN AND CORD.

Larger or smaller holes may be found in the brain tissue from dilatation of the perivascular lymph-spaces, or well-formed cysts may exist as a result of hemorrhage, inflammatory softening, hydatids, etc.

In cases of infection with Bacillus aërogenes capsulatus, gas may form in the brain and produce cavities, a condition known as *Swiss-cheese* brain.

Porencephalus is a term which has had a wide range of application to various defects of the brain substance. By some writers the term has been used to cover almost any congenital absence of brain tissue. By others, brain defects not congenital are included. Its most common application is to certain quite well-defined congenital conditions in which there is an absence of a considerable portion of one or both hemispheres. These may be produced in intrauterine life or post-partum by trauma or by chronic inflammation causing necroses.[1] The holes may lie deep in the substance of the brain. More commonly they come to the surface making conical depressions in the cortex, which the dura mater bridges over, but into which the pia extends. There may or may not be communication with the ventricles. This condition may coexist with various

[1] *Dahlmann*, Ztschr. f. d. ges. Neurol. u. Psychiat., 1910, iii, 223; and *Schütte, E.*, Centralbl. f. allg. Path., 1902, xiii, 633 (bibl.); *Globus, J. H.*, Histopathology of porencephalus, Arch. Neurol. and Psychiat., 1921, vi, 652.

mental aberrations, spastic hemiplegia, hydrocephalus, etc. and may cause sudden death. Similar defects may occur in the cerebellum.

The form of cavity found in the brain after embalming is of medico-legal importance chiefly because of the necessity for distinguishing these artefacts from injuries to the organ during life. The pressure of the embalming fluid ruptures the walls of the smaller capillaries which have begun to soften as a post-mortem change, and distends the brain tissue so as to form spherical, oval, or lenticular cavities. If a microscopic section of the wall of one of these cavities is made, it will be found that the glia and ganglion cells are perfectly normal in their structure quite

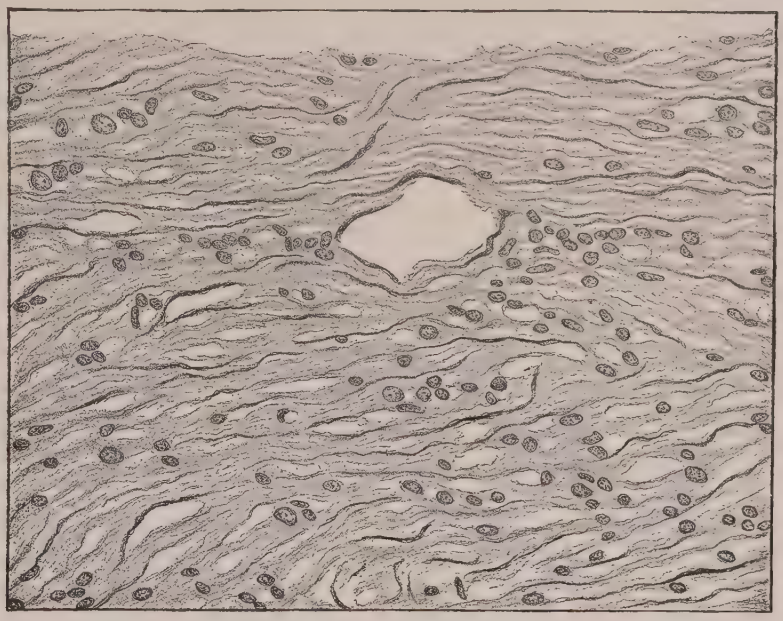


Fig. 815.—Traumatic Cavities in Brain.

Produced post-mortem by injection of embalming fluid. At the upper edge of the cut is the wall of a large cavity. A smaller cavity is seen just below. The cells at the edges of the cavities are perfectly preserved.

to the edge of the cavity (Fig. 815). This is proof that the formation of the cyst could not have been ante-mortem, as in this case the nutrition of the cells would have been seriously interfered with, even after a few hours. The fact that the contents of the cyst are clear and not blood-tinged, is an additional proof that the cavity was formed post-mortem.[1]

Cysts in the cord may occur as a result of softening or from unknown causes. Sometimes very long, narrow canals are found in the spinal cord, even reaching nearly its whole length. Some of these are evidently the dilated central canal, as they are lined with epithelium. Others, however, doubtless originate in hemorrhages (see Hematomyelopore, page 1150).

[1] For a case of formation of cysts post-mortem by gas bacilli, see *Pick, A.*, Arch. f. Psychiat.,1890, xxi, 910. For other types of post-mortem cyst formation, see *Hartmann*, Wien. klin. Wchnschr., 1900, xiii, 963 (bibl.).

GLANDULAR APPENDAGES OF THE BRAIN.

Pineal Gland. (Epiphysis Cerebri.)

The pineal gland is a small reddish body of a flattened oval shape, measuring 5 by 7 millimeters. It is derived from a diverticulum of the roof of the third ventricle. Microscopically, it is composed of a number of hollow follicles lined with epithelium and separated from each other by a vascular connective tissue. There are also a few neuroglia cells, ganglion cells, and sympathetic nerve fibers.[1] After the sixth or seventh year, the gland undergoes an involutionary process, the ganglion cells disappearing and the connective-tissue cells increasing and showing some hyaline degeneration; the glandular tissue also is diminished in quantity. The areas lined by ependyma extend and form small cysts. Much calcareous material is present in the gland in the adult.

Cysts of the epiphysis are frequently found and are usually connected with some hypertrophy, and hemorrhages into the substance have been noted. The function of the organ is still undetermined. Adiposity, early sexual maturity, and cachexia have been seen in connection with tumors of the gland, but the possibility that the first two of these conditions are due to a coincident alteration of the hypophysis must be considered.[2]

Up to the present time some seventy tumors have been reported. The tumors are of various types. **Teratomata** containing epidermis, hair, sebaceous glands, cartilage, fat, and smooth muscle have been seen in a number of instances, and are due to congenitally displaced fragments left during the closure of the medullary plates Other tumors have been described as **adenoma, sarcoma, glioma,** ependymal **neuroglioma,** and primary **chorionepithelioma.**[3] A number of the tumors are endothelial in type and are composed of spindle cells arranged in whorl-like masses, often inclosing psammomatous particles. The tumors of the gland do not, as a rule, form metastases.[4] An important secondary symptom is hydrocephalus, due to obstruction of the outflow of the cerebrospinal fluid.

Pituitary Body. (Hypophysis Cerebri.)

This is a small, reddish gray mass, oval in shape, which occupies the sella turcica of the sphenoid bone.[5] It consists of two lobes, the anterior being the larger. This is a prolongation from the buccal cavity and is formed of epithelium arranged in trabeculæ. It is richly supplied with blood-vessels in the form of the sinusoidal capillaries. Three types of cell are present: a granular, chromophilic variety staining darkly with eosin, and a non-granular basophilic type which stains deeply with meth-

[1] *Tilney, F.*, and *Warren, L. F.*, Morphology and Emotional Significance of the Pineal Body, Philadelphia, 1919.

[2] *Goldzieher*, Über ein zirbeldrüsengeschwulst, Virchows Arch., 1913, ccxiii, 353.

[3] *Askanazy*, Verhandl. d. deutsch. path. Gesellsch., 1906, x, 58; and *Rohdenburg, G. L.*, Proc. New York Path. Soc., 1917, xvii, 68.

[4] For a study, with bibl., of tumors of the pineal gland, see *Bailey* and *Jelliffe*, Arch. Int. Med., 1911, viii, 851. See also résumé by *Dana* and *Berkeley*, Med. Record, 1913, lxxxiii, 835; and *Schüller, A* Lewandowsky, Handb. d. Neurol., 1913, iv, 337 (bibl.).

[5] *Tilney, F.*, Contribution to the study of the hypophysis cerebri, with especial reference to its comparative histology, Mem. of the Wistar Institute of Anat. and Biol., Philadelphia, 1911, No. 2.

ylene blue. The third form does not take either stain deeply. The eosinophile cells are increased in acromegaly.

The posterior lobe is developed as a hollow downgrowth from the third ventricle. In adult life in man it is not connected with the ventricle. It contains neuroglia cells and nerve fibers.

Between the two lobes is the pars intermedia, sometimes described as a separate lobe, which contains both epithelial cells and neuroglia. Colloid-like material may occupy the spaces between the cells in this situation.

The hypophysis is closely correlated with various diseases of the skeleton and organs of the body, among them adiposity, gigantism, acromegaly, and some forms of infantilism.[1] Regressive changes in the gland are frequent; the connective tissue may be increased. Cysts may appear in the substance of the gland, and in the condition known as struma the colloid material is increased. Lime salts also collect in the substance of the gland and form small granules.

The most frequent tumor of the hypophysis is described as **adenoma.**[2] Tumors of this type are almost constantly found in connection with acromegaly.[3] The usual type of adenoma is that derived from the eosinophile cells, but the basophile cells also may form tumors.[4]

Carcinoma (Fig. 816) and **sarcoma** are seen, though infrequently; **lipoma** and **cystic teratoma** have been described. The embryological connection of the anterior lobe with the pharynx offers an explanation

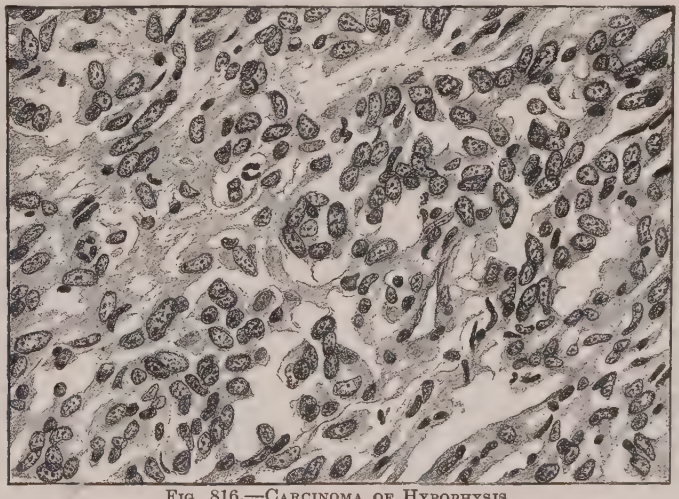


FIG. 816.—CARCINOMA OF HYPOPHYSIS.

for the squamous-cell epitheliomata and carcinomata which occur in the hypophysis.[5] **Cholesteatoma** also has been seen.

Echinococcus and other cysts may occur.[6] Gummata and tubercles are very rarely seen.[7]

[1] For further details, see discussion of these diseases in chapters on General Diseases and on Bone. See also *Cushing, H.*, The Pituitary Body and its Disorders, Philadelphia, 1912; *Wood, F. C.*, Hypophysis cerebri, Reference Handbook of the Medical Sciences, 1915, v, 469; *Biedl, A.*, The Internal Secretory Organs, New York, 1913; and *Falta*, Die Erkrankungen der Blutdrüsen. Berlin, 1913.

[2] *Löwenstein, C.*, Virchows Arch., 1907, clxxxviii, 44 (bibl.).

[3] *Petrén, K.*, Virchows Arch., 1907, cxc, 1 (bibl.).

[4] *Erdheim, J.*, Frankfurt. Ztschr. f. Path., 1910, iv, 70.

[5] *Bregman, L.*, and *Steinhaus, J.*, Virchows Arch., 1907, clxxxviii, 360.

[6] For a study of cysts of the hypophysis, see *Kanavel, A.*, Surg., Gynec., and Obst., 1918, xxvi, 61.

[7] For a case of gumma of the hypophysis, see *Weigert, C.*, Virchows Arch., 1875, lxv, 223.

PART III.

THE METHOD OF MAKING POST-MORTEM EXAMINATIONS.

CHAPTER I.

THE METHOD OF MAKING POST-MORTEM EXAMINATIONS.

General Considerations.

The object in making a post-mortem examination may be to determine whether a person has died from violence or poisoning; to account for a sudden death; or to study the lesions of disease. In any case the examination should include all the important parts of the body, not merely a suspected organ, and the results should be recorded at the time the examination is made.

Great care is necessary in endeavoring to ascertain the cause of death when the clinical history is imperfect or unknown. Mechanical injuries which destroy life by abolishing the function of one of the important viscera, are relatively infrequent. Most of the lesions found after death are rather the marks of disease than the cause of death. We do not know, for example, how great a degree of meningitis, or of pneumonia, or of endocarditis, or of cirrhosis, or of nephritis necessarily leads to death; but it is certain that one patient may recover with an extent of lesion which is sufficient to destroy the life of another. So with accidents; there is often no evident reason why fractures of the skull or of the pelvis should destroy life, yet they usually do. In some of the infectious diseases, such as typhoid fever, the visible lesions cannot always be called the cause of death. Sudden deaths of persons apparently in good health are often particularly obscure. In many of them we have to acknowledge that we can find no sufficient cause for the death. This is of course due to our imperfect knowledge, but it is much better in such cases to avow ignorance than to attribute the death to some trifling lesion. The brain and the heart are the organs which are especially capable of giving symptoms during life, without corresponding lesions after death. Very well-marked cardiac or cerebral symptoms may continue for days or months, and apparently destroy life, and yet after death we find no corresponding anatomical changes.[1] But it should be remembered that recent advances in our knowledge of the cell, which an improved technique in hardening and preparation has greatly fostered, have already shown that under various abnormal conditions the cells, especially of the nervous system, may undergo morphological changes of great significance, without perceptible alteration in the gross appearance of the affected part, changes which even the microscopical examinations of the past have failed to disclose. So that while there often appears to

[1] See Sudden Death, p. 507.

be a wide discrepancy between symptoms and lesions, with the increase of knowledge the scope of this discrepancy is steadily narrowing. It is the novice in post-mortem examinations who is particularly apt to mistake for lesions ordinary post-mortem alterations or the effects of embalming processes.

The cause of death is not always to be found in the organ which is primarily affected or which shows the most pronounced lesions. Thus chronic diffuse nephritis may exist for years with more or less marked symptoms of disease. But death may finally be due to a weakened heart which was secondarily involved, or occur in uremic convulsions, the brain showing no lesions at all. It is desirable, therefore, and in the majority of cases possible, to differentiate between obvious lesions and the cause of death.[1]

External Inspection.

Before commencing the examination of the internal viscera an inspection should be made of the external surface of the body. The minuteness of this inspection will depend upon the character of the case. In the case of an unknown person, or of one suspected to have died from unnatural causes, it is necessary to search for and record not only all contusions, wounds, etc., their size, situation, and condition, but also deformities from disease and any physical peculiarities of hair, eyes, teeth, moles, etc., by which the person may be identified. In such cases it is well, if possible, to photograph, weigh, and measure the body. In cases of doubtful identity it is sometimes wise to make a wax or plaster cast of the outside of the teeth and jaws. In ordinary examinations we note the general nutritive condition of the body, and look for evidences of external injury, for skin diseases, ulcers, edema, gouty deposits, abscesses, enlarged lymph-nodes, etc. The external organs of generation should be searched for syphilitic lesions.

It is well to weigh the body, since the significance of the weight of the individual organs is often closely dependent upon the relationship of their weight to that of the entire body.

Cadaveric Lividity.—It is usual to find certain changes in the external appearances of the body, which are due to the cessation of life and the commencement of decomposition. We speak now of bodies which have not been buried, but which have been kept in the ordinary way, lying on the back, and loosely covered with a shroud or dressed with the ordinary clothing.

After life becomes extinct, and before the blood coagulates, it changes its position chiefly in two ways: first, it is driven by their contraction out of the arteries into the veins; second, it settles in the veins and capillaries of the more dependent parts of the body, inducing usually within a few hours after death a mottling of the surface with irregular

[1] It is obvious that lack of space prevents a full presentation of all phases of post-mortem technique; for fuller details the reader is referred to *Cattell, H. W.*, Post-mortem Pathology, 3d ed., Philadelphia, 1906; *Wadsworth, W. S.*, Post-mortem Examinations, Philadelphia, 1915; *Busse, O.*, Das Obduktionsprotokoll, 2d ed., Berlin, 1903; *Nauwerck, C.*, Sectionstechnik, 2d ed., Jena, 1894; and the texts on legal medicine (see page 481), which contain many hints and procedures of value in the examination of the bodies of those who have died under suspicious circumstances.

livid patches. These patches may coalesce, forming a uniform dusky red color over the back of the trunk, head, and extremities, and sometimes over the ears, face, and neck. The same effect is observed on the anterior aspect of the body if it has lain on the face. At points of pressure, from folds in the clothing, or from the weight of the body on the table, the red color is absent or less marked. These changes occur before putrefaction sets in. This cadaveric lividity or hypostasis should not be mistaken for ante-mortem ecchymosis, from which it may usually be readily distinguished by its position and extent, by the fact that the surface of the skin is not elevated, and by the fact that on incision no blood is found free in the interstices of the tissues. Not infrequently the subcutaneous tissue in the vicinity of these post-mortem hypostases becomes infiltrated with reddish serum. Very soon after death, particularly in warm weather, the tissues immediately around the subcutaneous veins of the neck and thorax, and in other situations, may be stained a bluish red color from the decomposition and escape from the vessel of the coloring matter of the blood. If the epidermis has been detached at any point, the skin beneath soon becomes dry and brown.

Putrefactive Changes.—Usually in from one to three days, depending upon circumstances, a greenish discoloration of the skin appears, at first upon the middle of the abdomen, over which it gradually spreads, assuming a deeper hue and often changing to a greenish purple or brown. Greenish patches may now appear on different parts of the body, earliest upon those overlying the internal cavities; this discoloration is probably produced by the action on the hemoglobin of gases developed by decomposition. The eyeballs now become flaccid, and if the eyelids are not closed the conjunctiva and cornea become brown and dry. The pressure of gases developed by decomposition in the internal cavities not infrequently forces a greater or less quantity of frothy, reddish fluid or mucus from the mouth and nostrils, distends the abdomen, and, if excessive, may lead to changes of position of the blood in the vessels, and even a moderate amount of displacement of the internal organs.[1]

After a varying period, sometimes within five or six days, the entire surface of the body may be discolored, green or brown. Then the epidermis may become loosened by the accumulation of gases and fluids beneath and the tissues become flaccid. The abdomen may be greatly distended and the features distorted from swelling. The rapidity with which these changes occur depends upon various conditions. Thus an elevated temperature and the presence of air and moisture hasten the advent and progress of putrefaction.

The bodies of infants usually decompose more rapidly than those of adults, fat bodies more quickly than lean ones. The infectious diseases, intemperance, and the puerperal condition promote rapid decomposition, as does also death from suffocating gases. Poisoning by arsenic, alcohol, antimony, sulphuric acid, strychnine, and chloroform may retard the

[1] With early and marked formation of gas in the tissues and organs, especially in the liver, the possibility of infection with Bacillus aërogenes capsulatus should be borne in mind. See p. 327.

progress of decomposition. Burial in dry soil and submersion in water also retard the progress of decay.[1]

Cooling of the Body.—After death the chemical changes upon which the maintenance of the temperature depends rapidly diminish, and the body gradually cools to the temperature of the surrounding medium. This usually occurs in from about fifteen to twenty hours, but the time required depends upon a variety of conditions. Immediately after death there is, in nearly all cases, a slight elevation of internal temperature, owing to the fact that the metabolic changes in the tissues still continue for a time, while the blood ceases to be cooled by passing through the lungs and peripheral capillaries. After death from certain diseases—yellow fever, cholera, rheumatic fever, and tetanus—a considerable elevation of internal temperature has been repeatedly observed. The time occupied by the cooling of the body may be prolonged after sudden death from accidents, acute diseases, apoplexy, and asphyxia. A number of cases are recorded in which the body retained its heat for several days, without known cause.

After death from wasting chronic disease, and in some cases after severe hemorrhages, the cooling of the body is very rapid, the interior temperature being reduced to that of the surrounding air within four or five hours. Fat bodies cool less quickly than lean ones, the bodies of well-nourished adults less quickly than those of children or old persons. The temperature of the surrounding medium, and the degree of protection of the body from currents of air, of course, modify the progress of cooling; and the internal organs naturally retain their heat longer than the surface of the body. The rate at which cooling occurs is most rapid, as a rule, during the hours immediately following death, notwithstanding the post-mortem rise which may ensue.

It will thus be seen that, if required to pronounce upon the time which has elapsed since death in a given case, we can do so only approximately. It is necessary to take into account all of the above-mentioned conditions which modify the rate of cooling of the body, and then we may be able to state only the probabilities of the case. It is furthermore unsafe in any case to infer the cause of death from the rate of cooling of the body.

Rigor Mortis.—Death is usually succeeded immediately by a period of complete muscular relaxation. The jaw drops and the limbs become flaccid. The muscles may retain for two or three hours, however, the capacity of contracting, on the application of appropriate stimuli. On the average, within six hours the muscles become firm and rigid. This post-mortem rigidity is called *rigor mortis*. On the occurrence of the rigor mortis the muscles become fixed in whatever position they may have had at the time of its occurrence. It usually begins in the muscles of the eyelids, extends to those of the back of the neck and lower jaw,

[1] For a study of bacteria in the blood of the cadaver, see *Löw, L.*, Ztschr. f. Heilk., Abth. f. path. Anat., 1900, xxi, 47. See also *Babes*, Ann. d'hyg. pub., 1899, xli, 193.

Concerning the conversion of the body into adipocere, see *Ewing*, Peterson and Haines, Text-book of Legal Medicine, Philadelphia, 1904, i, 138; see also *Ascarelli*, Vrtljschr. f. gerichtl. Med., 1906, xxxii, 219; *Müller*, Post-mortem Decomposition, etc., Zurich, 1913; and *Ruttan, R. F.*, and *Marshall, M. J.*, Jour. Biol. Chem., 1917, xxix, 319.

then to the face and neck, and thence passing downward affects the muscles of the thorax and lower extremities. It usually disappears in the same order. Although commencing on the average six hours after death, it may set in at once or be delayed for twenty-four hours or more. It may pass off very rapidly, in rare cases in from one to three hours; or it may persist for two or three weeks or longer. It may be said in general that the average time of its disappearance is within twenty-four or forty-eight hours after its occurrence, depending on temperature, its intensity, the mode of death, the period of its advent, etc. Caspar states that in fetuses before term he has never observed rigidity, and that in young children it is feeble and of short duration. Its occurrence and phenomena may be in some cases of the highest medicolegal importance; but its careful observation does not, with our present knowledge of its significance, appear essentially to further the aims of the practical pathologist.[1]

Contusions.—It is often important to determine whether violence has been inflicted upon a body before death. In regard to this point, we must remember, first, that blows and falls of sufficient violence to fracture bones and rupture the viscera may leave no marks on the skin, even though the person has survived for several days; and, second, that there are post-mortem appearances which simulate ante-mortem bruises. A severe contusion during life may present, at first, no mark or only a general redness. After a short time the injured part becomes swollen and of a red color; this color may be succeeded by a dark blue, and this in turn fade into a greenish yellow or yellow; these later appearances are due to an escape of blood from the vessels and to a subsequent decomposition of hemoglobin. If, therefore, we cut into such an ecchymosis after death, we find extravasated blood or the coloring matter of the blood, in the form of pigment granules, free in the tissues. Post-mortem discolorations, on the other hand, although their external appearance may resemble that of ante-mortem ecchymosis, are not formed by an extravasation of blood, but by a circumscribed congestion of the vessels or by an escape of blood-stained serum. If we cut into such discolorations, therefore, we find no blood outside the vessels. Care should be taken not to mistake the lesions of hemorrhagic infection for traumatic ecchymoses.

Blows on the skin of a body which has been dead for not more than about two hours may produce true ecchymoses with extravasation of blood, such as can be distinguished with great difficulty or not at all from those formed during life. If putrefactive changes be present, the difficulty of distinguishing between ante-mortem and post-mortem bruises is greatly enhanced.

Hanging and strangulation are attended with the formation of marks on the neck which are described in works on forensic medicine. These marks must not be confounded with the natural creases of the skin of the neck. Many adults during life have creases of the skin of the neck,

[1] For further details concerning rigor mortis, putrefactive changes, particularly the later stages, and the phenomena of cooling of the body, see *Tidy, C. M.*, Legal Medicine, Philadelphia, 1884, vol. i, or other works on medical jurisprudence.

one or more in number, running downward from the ear under the chin or encircling the neck. After death these creases may be much more evident than during life, and may be rendered more decided by the position of the head and the freezing of the body. They usually persist until the skin putrefies.

Wounds.—We should notice the situation, extent, and direction of a wound, the condition of its edges and the surrounding tissues. If it be a deep, penetrating wound, its course and extent should be ascertained by careful dissection rather than by the use of a probe.

If the edges of a wound be inflamed and suppurating, or commencing to cicatrize, it must have been inflicted some time before death. In a wound inflicted a short time before death, the edges are usually everted; there may be more or less extravasation of blood into the surrounding tissues, and the vessels may contain coagula; but sometimes none of these changes are observed. The chief characteristics of a wound inflicted after death are absence of a considerable amount of bleeding, non-retraction of the edges, and the absence of extravasation of blood into the tissues. But a wound inflicted within two hours after death may resemble very closely one received during life. In general, unless a wound is old enough for its edges to present inflammatory changes, we must be very careful in asserting its ante-mortem or post-mortem character.

Fractures.—It may be important to determine whether a bone was fractured before or after death. This point cannot always be decided. Fractures inflicted during life are, as a rule, attended with more extravasation of blood and evidences of reaction in the surrounding tissues; but fractures produced within a few hours after death may resemble these very closely. Usually a greater degree of force is necessary to fracture bones in the dead than in the living body.

Scars and Tattoo Marks.—The presence and character of cicatrices should be noticed. Scars produced by any considerable loss of substance may become very much smaller and less conspicuous, but never entirely disappear. Slight and superficial wounds, however, leave marks which may not be permanent. The discoloration produced by tattooing may, although it rarely does, disappear during life.

Internal Examination.[1]

After completing the external inspection of the body, we commence the internal examination. In order that this examination may be made both thoroughly and rapidly, we should follow a regular method which should be such as will enable us to examine the relations of parts to one another, without seriously disturbing them, and to remove and inspect the organs in such an order and manner as will not interfere with the examination of parts which are to follow. In certain cases it may be necessary to depart from the regular method;[2] but, as a rule, the following plan will be found most advantageous.

[1] For sizes and weights of various organs, and other data, see *Vierordt*, Anatom., Physiol., und Physikalische Daten u. Tabellen, 3d. ed., 1906. For a study of the weights of the viscera in infancy and childhood, see *Bovaird* and *Nicoll*, Arch. Pediat., 1906, xxiii, 641.

[2] Sometimes the thoracic or abdominal viscera or both together may wisely be taken out in mass. See, for advantages of this method, *Heller, G.*, Vrtljschr. f. gerichtl. Med., 1904, xxvii, 110.

It is important to remember the difference between the distribution of the blood in the body during life and after death. During life the blood is in constant motion and is distributed in a regular way in the heart, capillaries, arteries, and veins. Inflammations and obstructions to the circulation may disturb this natural distribution and produce congestion of particular parts of the body. After death the blood ceases to circulate; it leaves the left cavities of the heart, the arteries, and capillaries, and collects in the veins and the right cavities of the heart. According to the character of the disease which causes death, coagulation of the blood takes place more or less extensively and at an earlier or later period. The local congestions which existed during life often disappear after death. On the other hand, local congestions are found after death which did not exist during life. Thus, after death the scalp often contains a large amount of venous blood. The veins of the pia mater and the sinuses of the dura mater may be filled with blood. The mucous membrane of the larynx and trachea may appear to be deeply congested. The lungs are congested if the patient has been comatose for some hours before death. All the tissues of the back and the membranes of the spinal cord are often gorged with venous blood. The right auricle and ventricle of the heart may contain fluid or clotted blood in considerable quantity.

THE HEAD.

The scalp is divided by an incision across the vertex, from ear to ear. The flaps are dissected forward and backward, taking up the temporal muscles with the skin and leaving the pericranium attached to the bone. The internal surface of the scalp and the pericranium are to be searched for ecchymoses and inflammatory lesions.

A circular incision is now made through the cranium with a saw. The incision should, in front, pass through a point about eight to ten centimeters above the bridge of the nose; behind, through the occipital protuberance. Care should be taken not to cut through the dura mater with the saw. When the roof of the cranium is thus entirely loosened, a stout hook is introduced under the upper edge of the calvarium, and this is wrenched off with a jerk. Some pathologists prefer to make two incisions meeting in blunt angles just above and posterior to the external auditory canal. The cosmetic effect is then better, as the calvarium is more firmly fixed when the body is prepared for burial.

Sometimes the dura mater is so firmly adherent to the calvarium that the latter cannot be torn from it without injury to the brain. In this case, and also if the dura mater should have been accidentally cut through by the saw in making the circular incision, the dura mater may be cut through at the level of the cranial incision, and the brain removed with the calvarium and separated afterward. Or, which is better, in addition to the circular incision, a longitudinal incision may be made, from front to back, about three-quarters of an inch to one side of the median line of the skull, and a segment of bone removed. The knife blade may

then be inserted from the open side, and the dura cut away from the skull-cap along the line of the longitudinal sinus, where the adhesions are apt to be most firm.

We should notice whether or not the calvarium is symmetrical. The cranial bones increase in size by a growth of bone at the edges of the sutures. If any suture becomes completely ossified and closed prematurely, the bones will be unequally developed. The thickness and density of the cranial bones vary considerably within the limits of health. There are often deep depressions on the inner surface of the skull along the sagittal suture, caused by the pressure of the Pacchionian bodies, and of no pathological significance. We should observe the blood content of the bone, determine the existence or absence of fractures, inflammatory lesions, exostoses, etc.

The dura mater is now exposed. It is more or less adherent to the calvarium; a moderate amount of adherence, especially in old persons, does not denote disease. Very extensive and firm adhesions are usually produced by inflammation. Near the median line the Pacchionian bodies often project through the dura mater and may produce indentations in the internal surface of the calvarium. We must look for clots and for tumors and for inflammatory lesions on the external surface of the dura mater. The longitudinal sinus should be laid open and its contents examined. A circular incision is then made through the dura mater in a line corresponding to the cranial incision; the falx is divided between the anterior lobes of the brain, and the entire membrane drawn back. We should observe the existence of abnormal adhesions of the dura mater to the pia mater, bearing in mind that a moderate amount of adhesion along the longitudinal fissure is normal. The internal surface of the dura mater is to be examined for the products of inflammation and for tumors.

The pia mater covering the convex surface of the brain is now exposed. The degree of congestion, and the existence of serum, pus, or blood, beneath, within, or upon it, are now to be ascertained before the brain is removed. The pia mater in old persons frequently loses its transparency and becomes thick and white; this change is most marked along the longitudinal fissure and large vessels. Marked and general thickening of the pia mater is the result of chronic inflammation. Along the longitudinal fissure, and sometimes at a considerable distance from it, we usually find small, elevated, whitish nodules, which are the *Pacchionian bodies* and are normal in the adult.

The amount of serum beneath the pia mater varies. A considerable amount, especially in cachectic persons, may exist without brain disease. Clear serum, raising the pia mater and separating the convolutions of the brain, may be simply dropsical or due to chronic meningitis. Turbid and purulent serum, beneath and in the pia mater, is due to acute or chronic meningitis. The degree of flatness of the surface of the convolutions should be observed before removing the brain; for, when marked, it affords an important indication of pressure, from hemorrhage, inflammatory products, internal fluid effusions, and tumors. The pia mater should be carefully examined for miliary tubercles.

The Brain.—After examining the convex surface of the brain, the anterior lobes of the cerebrum are to be pulled gently backward, the nerves, vessels, and tentorium severed, and the medulla cut squarely across, as low down as possible. The brain is now removed from the cranium by passing the fingers of one hand down, beneath, and behind the lobes of the cerebellum, and drawing the brain out, supporting the convexity with the other hand.

The adult brain in the male weighs on the average about 1,400 grams; that of the female, about 155 grams less. The average proportional weight of the brain to that of the body is about one-forty-fifth, although in this, as in the absolute weight, there is considerable variation.[1]

Fig. 817.—Side View of the Human Brain, Showing its Fissures and Convolutions.

The exact situation of any lesion which is apparent externally should be described by its relation to the lobes, fissures, convolutions, and sulci (Fig. 817).

The brain is first laid upon its convex surface, and the anterior, middle, and posterior cerebral arteries, as well as the basilar and the carotids, are first examined for emboli, thrombi, atheroma, and aneurysms. Evidences of extravasations of blood, tumors, and inflammatory lesions are next looked for. The brain is then turned over on to its base. An incision is made through the pia mater, over the convex surface of the cerebrum. The membrane is stripped up, and its adherence to the brain and its thickness are noted.

The more common method of opening the brain is as follows: The halves of the cerebrum are separated until the superior surface of the corpus callosum is exposed (Fig. 818). A longitudinal incision is made through the junction of the corpus callosum and the cerebrum, and downward into the ventricle. The incision should be made carefully, so

[1] For a study of the weight of the brain at various ages, see *Handmann, E.*, Arch. f. Anat. u. Physiol., Anat. Abth., 1906, Suppl., p. 1.

as not to cut through the ventricle into the ganglia below. The incision thus made through the roof of the ventricle is prolonged backward and forward in the direction of the cornua, so as to expose the entire ventricle. A longitudinal incision is then made outward and backward into the hemisphere, from the outer edge of the lateral ventricle nearly to the pia mater. A second incision is then made through this cut surface outward, and this is repeated until the hemisphere is divided into a number of long, prism-shaped pieces, held together by the pia mater

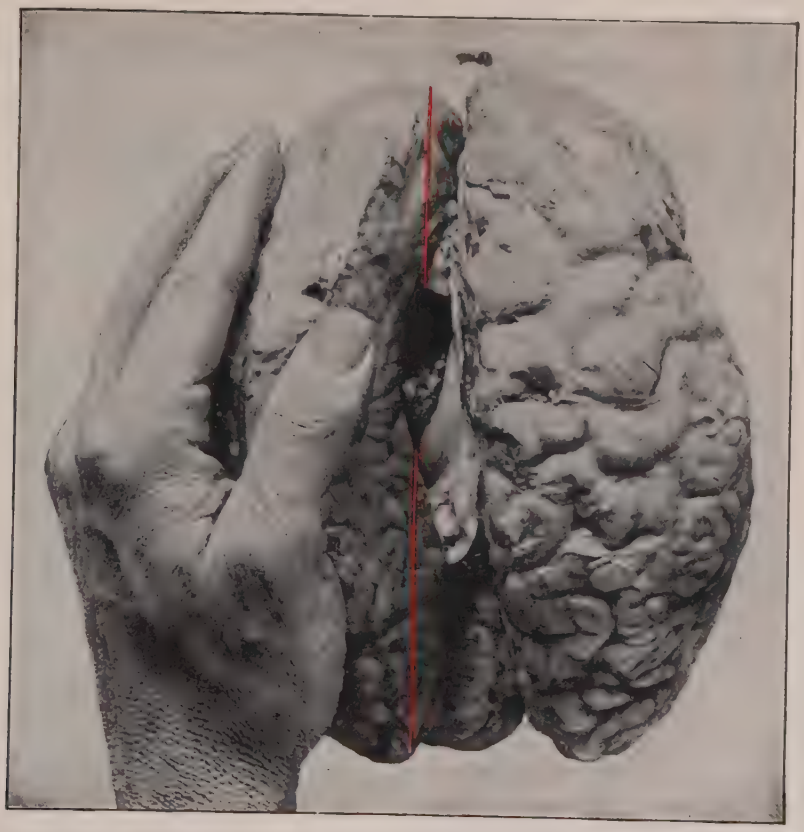


Fig. 818.—Method of Opening the Brain, Showing the Direction of First Incision.

and a small portion of the cortex. The brain is now turned around so as to bring the other hemisphere under the hand, and the operation is repeated on the other side.

The size, shape, and contents of the ventricles should be noticed, and the thickness and appearance of the ependyma.

The fornix and the central portion of the corpus callosum are cut across by passing the point of the knife through the foramen of Munro and cutting upward. They are then drawn backward, one of the posterior cornua of the fornix being severed and laid to one side. The

velum interpositum and the choroid plexus are now dissected up, the blood contents and the general appearance noted, and the third ventricle examined. Not infrequently small cysts of the choroid are found, which seem to have little or no pathological significance.

The fourth ventricle is now opened by a longitudinal incision through the vermiform process. Each hemisphere of the cerebellum is divided first into two parts, by an incision through the upper and inner convex border, and then each segment is further divided by incisions in the same direction.

Thin transverse sections are now made through the cerebral ganglia, commencing in front (Fig. 819). The ganglia are supported, and the sec-

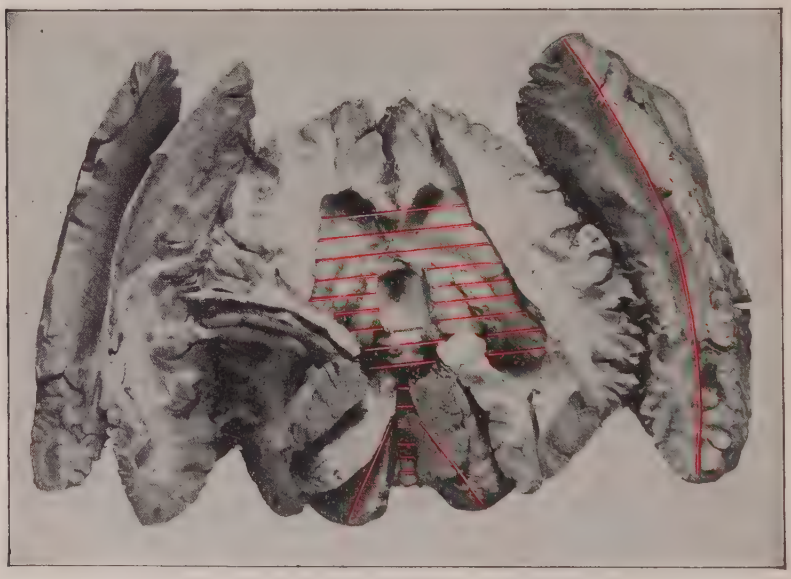


FIG. 819.—METHOD OF OPENING THE BRAIN, SHOWING THE UNFOLDED SEGMENTS OF THE CEREBRUM AND LINES OF TRANSVERSE INCISION OF THE BASAL GANGLIA AND DIRECTIONS OF THE INCISIONS OF THE CEREBELLUM.

tions caused to fall apart as they are cut, by carrying the fingers of one hand under the brain, and gently lifting the ganglia at points just beneath where the sections are made. It is important to observe the exact position of any lesions which may be discovered in the cerebral ganglia, and the relations of such lesions to the external and internal capsule and to the caudate and lenticular nuclei.

Finally, the segments of the cerebrum and cerebellum are folded up together into their original positions, the whole is turned over on to the vertex, and thin sections are made through the medulla. Small clots in the medulla should not be overlooked.

In case of the discovery of apoplectic clots, areas of softening, etc., either in the hemispheres or in the basal ganglia, after their location and extent are determined, they should be carefully searched for lesions of

the blood-vessels, minute aneurysms, areas of degeneration, and ruptures. For this purpose it may be necessary to allow a stream of water to run over the affected portion, so as to wash out the brain substance and expose the vessels. In some cases the blood-vessels are best exposed

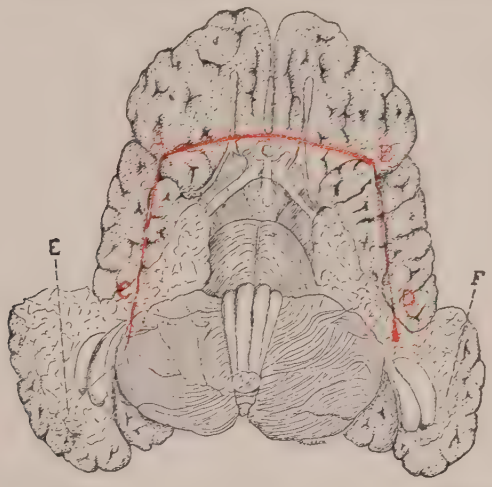


FIG. 820.—SCHEMATIC PICTURE OF BRAIN, SHOWING THE METHOD OF DISSECTION FROM THE BASE (Meynert's method).

E and *F*, Temporal lobes turned backward and outward; *AB*, *AC*, *BD*, line of incision to remove basal piece.

by macerating the brain tissue at the seat of the lesion for some hours in water, and then either washing out the brain substance under the faucet, or removing it by shaking the tissue in water in a closed vessel.

While the above mode of dissecting the brain gives a very complete view of the seat and extent of lesions in general, when a more exact localization of lesions with a microscopic examination is to be made, the following—called Meynert's method—is a better method of opening the brain:

FIG. 821.—THE BRAIN AXIS SEPARATED FROM THE BRAIN MANTLE, AS SEEN FROM ABOVE

After completing the external examination, as detailed above, the brain is laid on its vertex, the cerebellar end toward the operator. The cerebellum is raised by the fingers of the left hand, and the pia cut through along the sides of the corpora quadrigemina, around the crura and along the inner margins of the temporal lobes, to the middle cerebral artery on both sides (Fig. 820). Then, raising the temporal lobes, in turn, by their apices, the pia is cut through along the course of the middle cerebral artery into the Sylvian fissure, and along the course of its posterior branch to its end. Now, drawing the temporal lobes one after the other upward and outward, their junction with the

base is cut, the knife being held horizontally so as not to injure the basal ganglia until the descending horn is opened. The point of the knife being in the descending horn, the incision through the brain substance then passes outward and backward well into the posterior horn, thus partially severing the lateral surface of the brain, the junction of the occipital and temporal lobes. The temporal lobes are then turned outward and backward (Fig. 820).

The operculum is now pulled well outward, completely exposing the island of Reil, and a slightly curved transverse incision is made, deep enough to pass into the anterior horns of the ventricles, connecting the anterior sulci of the island of Reil (Fig. 820, *A*, *B*).

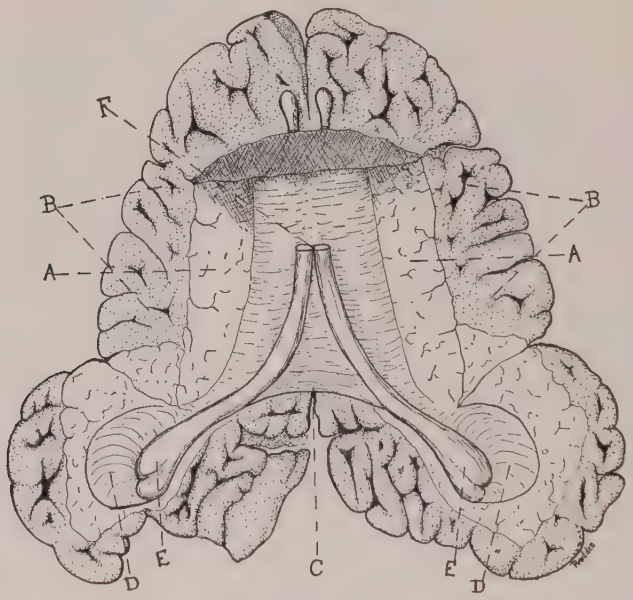


Fig. 822.—The Brain Mantle, as Seen from Below.

A, Internal capsule; *B*, operculum; *C*, posterior border of corpus callosum; *D*, descending horn; *E*, cornu Ammonis.

The cerebellum is now raised, and the point of the knife inserted into the ventricle, then with short incisions from within outward, the internal capsule on either side from back to front (Fig. 820, *CA* and *DB*) is cut through, care being taken not to injure the basal ganglia. Then the crura of the fornix and the septum lucidum are cut across, the fornix being left lying on the corpus callosum.

The square basal piece (Fig. 821) thus freed—*the brain axis*—includes the island of Reil, the basal ganglia, the crura, pons, medulla, and cerebellum. The remaining portion—*the brain mantle*—includes the convolutions, corpus callosum, and fornix (Fig. 822).

The basal piece may be further examined by a series of transverse incisions, from one-half to three-quarters of an inch apart, and it may be

hardened either with or without the cerebellum. The convolutions may be cut into small pieces by longitudinal and transverse incisions, made from within and not reaching quite to the pia mater, which will then serve to hold the pieces together in their proper relations to one another.[1]

The Base of the Cranium.—We now return to the skull. The remaining sinuses of the dura mater should be opened, and this membrane then entirely stripped from the bone. The bones at the base of the skull are to be examined for fractures, inflammatory lesions, and tumors. In cases of acute purulent meningitis, the temporal and frontal bones should be carefully examined, as the inflammatory process is sometimes transmitted from the internal ear, or mastoid cells, or frontal sinuses.

The eyes may be removed by breaking the roof of the orbit with a hammer, removing the fragments of bone, and dissecting away bone and muscles, so as to expose the optic nerve and posterior segment of the eye. That portion of the globe which is not covered by conjunctiva can now be cut away with scissors and removed with the optic nerve, or, when permissible, the whole eye may be cut out.

The examination of the internal ear may be made by removing its entire bony encasement with the saw and chisel, or by the exposure of special parts by hammer and chisel, and by suitable opening of the removed parts with a fine saw.

Hardening and Preservation of the Tissues for Microscopical Examination.

For the study of *tumors* and *inflammatory lesions* of the bones of the skull and ossifications of the dura mater and pia mater, the affected portions should be cut into small pieces, fixed in 4 per cent. formaldehyde, Bouin's, or in Orth's fluid, and decalcified. The dura mater should be stretched on a flat piece of wood or cork with pins, before hardening.[2]

The *pia mater* is so delicate that if it is separated from the brain when quite fresh its tissues are apt to be injured. The portions of the pia mater which are to be preserved should therefore be removed by cutting off slices of the brain substance about half an inch thick, with the membrane still attached, and placing the whole in Orth's fluid. After twenty-four hours, the pia mater will have become sufficiently hard to permit of its being stripped off without injury, and it is then spread loosely on a flat cork with pins, the free surface outward, and the cork floated, specimen side down, in 80 per cent. alcohol, changing to strong alcohol after twenty-four hours.

When sections showing the pia in its relationship to the underlying brain tissue are required, small blocks of the brain and pia together should be cut out and hardened in Orth's fluid or in 4 per cent. formaldehyde.

When the *ependyma* is to be studied apart from the associated nerve tissue, it may be sliced off with a sufficient quantity of underlying brain substance to prevent its folding, and hardened in Orth's fluid. The *brain* may be hardened in Orth's fluid, in 95 per cent. alcohol, or in 4 per cent. formaldehyde. The pieces of brain tissue should not be more than 1 cm. thick; it is better if they are thinner than this. They should be suspended in gauze or rest upon a layer of absorbent cotton on the bottom of the jar, the pieces, if these are numerous, being held apart by a little cotton. Thus the preservative fluid, which should be abundant, is in contact with the surfaces of the pieces of tissue. Ordinarily, with a change of fluid on the second day, the fixation by formaldehyde or Orth's fluid is complete in a week, when the fixatives are thoroughly

[1] For further details of this method of opening the brain, and a consideration of its advantages, see *Van Gieson, I.*, New York Med. Jour., 1889, l, 57.

[2] For details of the methods, see *Mallory* and *Wright*, Pathological Technique, 8th edition, 1924.

washed out and replaced by 50 per cent. alcohol, which, in turn, is replaced after forty-eight hours by 80 per cent. or by 95 per cent. alcohol.

When *degeneration* in nerves is to be studied, the specimens of nerve tissue may, by Marchi's method, be hardened for a week in Müller's fluid, and then transferred to the following solution:

Müller's fluid	2 parts.
Osmic acid, 1 per cent.	1 part.

After a week the specimens are washed and transferred to 95 per cent. alcohol. In such specimens the fat droplets in the degenerated areas are black, while the myelin is yellowish in color.

Certain lesions, particularly the softenings of the brain, are best studied by teasing, when fresh, in 0.5 per cent. solution of sodium chloride, or in frozen sections of the fresh tissue. The blood-vessels may be stretched on cork with pins and hardened with Orth's fluid or formaldehyde. The eye and portion of the optic nerve, if removed, should be fixed by Orth's fluid and the hardening completed by alcohol.

For many methods of fixation and study which are useful for special purposes, we refer to special works on technique.

THE SPINAL CORD.

The examination of the spinal cord is usually most conveniently made after the removal of the brain.

The body should be placed face downward, with a block under the thorax and the head hanging over the edge of the table. An incision is made through the skin and muscles along the entire length of the spine, and the soft parts are dissected away on each side so as to expose the laminæ of the vertebral column. The laminæ are then divided, close within the articular processes, with the saw.

The saw should be so directed in severing the laminæ that the incision shall touch the outer border of the spinal canal, as otherwise the laminæ and spinous processes are not easily separated. Great care should be taken on the one hand not to injure the cord with the saw, and on the other completely to loosen the portions of bone to be removed. These, which are the spinous processes and laminæ, are now torn away together, with a stout hook, exposing the cord.

By means of a long, curved chisel, made for this purpose, the bodies of the vertebræ may be removed from the front after the thoracic and abdominal viscera are taken out, and the cord thus exposed and removed. But in this anterior method of removing the cord, as well as by the use of chisel and mallet, bone-shears, etc., in the ordinary method, there is great liability of injuring the delicate tissues of the cord and producing, as Van Gieson has shown,[1] mechanical alterations which are likely to be mistaken for malformations or the results of disease.

When the body has lain on the back, the membranes of the cord may be found considerably congested, without indicating the pre-existence of disease. If the body has lain for some time, especially in warm weather, serous fluid may have accumulated within the membranes, as a result of post-mortem change.

[1] *Van Gieson, I.*, New York Med. Jour., 1892, lvi, 337, 365, 421.

The roots of the nerves are now to be cut across, as far away as possible from the cord, and the cord removed in its membranes, care being taken not to press it in any way. It is the safest plan not to grasp the cord itself, but with a forceps to seize the dura mater and thus lift it up at once as it is freed from its attachments. It is now laid on the table,

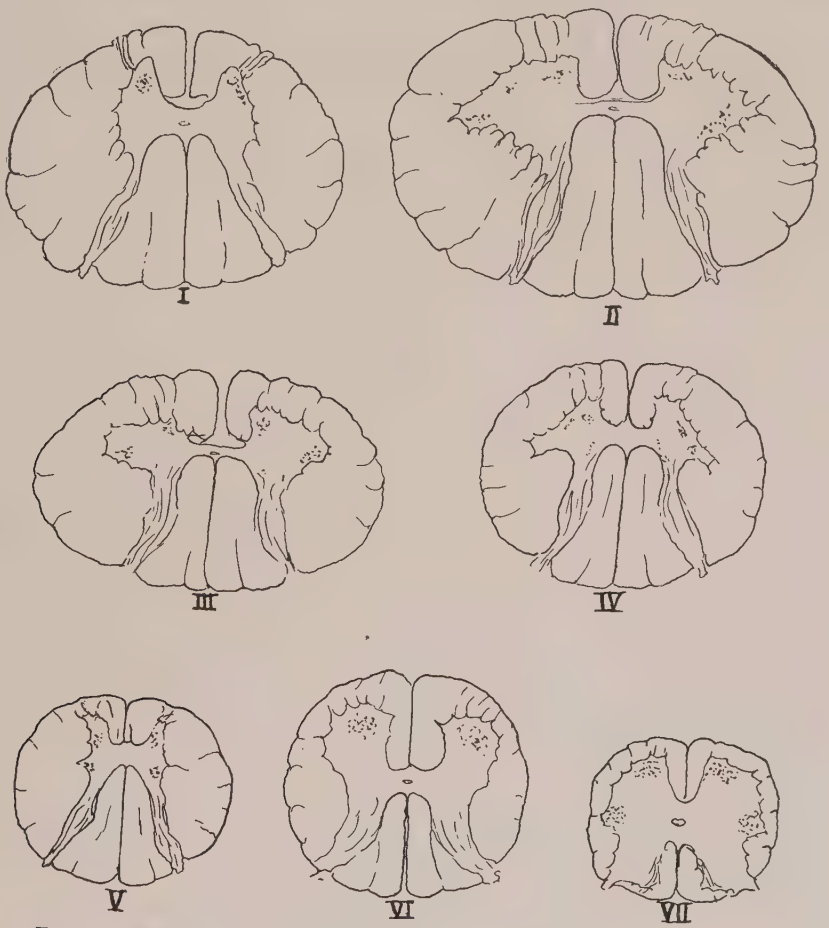


FIG. 823.—OUTLINES OF SECTIONS OF THE SPINAL CORD AT DIFFERENT LEVELS.

Copies of these outlines may be used for memoranda of the situation of lesions of the spinal cord. *I*, Second cervical; *II*, fifth cervical; *III*, eighth cervical; *IV*, first dorsal; *V*, eighth dorsal; *VI*, third lumbar; *VII*, fourth sacral.

and the dura mater laid open with scissors on the anterior and posterior surfaces over its entire length, and searched for tumors, inflammatory lesions, etc. The finger should be passed gently along the cord as it lies on the table, so as to detect any marked softening or sclerosis. The weight of the spinal cord is from 30 to 38 grams. It should now be held lightly over the fingers, and smooth transverse incisions made, with a

very sharp knife or razor, about half an inch apart through its entire substance between the segments, leaving these attached to the pia mater.

The segments of the spinal cord are those parts from which the spinal nerves arise, and it is convenient for the location and description of lesions to number the segments in correspondence with the nerves which arise from them, and to indicate on outline diagrams of the cord (Fig. 823) the exact seat of small lesions.

The cut surfaces should be carefully examined for abnormal blood contents, hemorrhages, inflammatory lesions, softening, scleroses, and pigmentations. Important lesions of the cord may be invisible to the naked eye, and hence, if disease be suspected, the organs should be preserved for microscopical examination. The spinal ganglia may now be removed and preserved for further examination. After removal of the cord, fractures and displacements of the vertebræ are easily recognized.

Preservation of the Spinal Cord and Its Membranes, and of Peripheral Nerves.—After the removal of the spinal dura, the entire cord with its nerve roots—the segments into which it has been cut for gross examination being left in place—should be laid on a wad of absorbent cotton in a large jar of Orth's fluid or formaldehyde, the segments being slightly separated from each other by a little absorbent cotton. Van Gieson recommends the careful rolling of the segmented cord into a loose spiral and laying this coil on a wad of absorbent cotton in the fixative. In this way the cut ends of the segments are held apart, accessible to the fluid, and harden with little distortion.

The hardening and preservation of the cord may be done by the same methods as suggested above for the brain. If the dura mater of the cord alone is to be preserved, it should be treated in the manner suggested for the dura mater cerebralis. The pia mater spinalis is best studied in sections through the entire cord, the membranes being left in situ.

Peripheral nerves may be hardened in Orth's fluid or in formaldehyde.

For the hardening of the peripheral nerves, osmic acid is very useful, especially when changes in the myelin are to be sought after. As osmic acid does not readily penetrate the lamellar sheath so as to come in contact with the nerve fibers, in trunks of any considerable size, the following procedure, as suggested by Van Gieson, will be found useful: A piece about one-half inch long is cut from the nerve to be examined; one end of this segment is held with a forceps, while with another forceps the individual nerve fibers, or small clusters of these, are pulled out of the lamellar sheath and put at once in a 1 per cent. aqueous solution of osmic acid, in which they remain twenty-four hours, and are then washed and transferred to glycerin, to which 25 per cent. alcohol is added. In this mixture they may be preserved. Marchi's method is useful for the study of degeneration in peripheral nerves.

THE THORAX AND ABDOMEN.

The body is replaced on its back, and a single straight incision is made from the top of the sternum to the pubes, passing to the left of the umbilicus. For this purpose a large knife should be used, held firmly in the whole hand, and the movement should be mainly from the shoulder. The first incision should divide everything down to the sternum and peritoneum. A short incision should then be made through the peritoneum, just below the ensiform cartilage. Into this opening two fingers of the left hand are introduced and separated from one another, and, the parietes being raised and the sides of the opening being held

apart by the fingers, the peritoneum is divided to the pubes, care being taken to hold the knife horizontally so as not to cut the intestines. The skin and muscles are then dissected off from the thorax on both sides as far back as the false ribs.

This dissection should be made by long sweeps of the knife, which should be made to cut with the full blade and not with the point only; and if the skin and muscles be pulled strongly away from the chest with the left hand, it may be done very rapidly and with a few strokes of the knife. We notice here the amount of subcutaneous fat and the condition of the muscles. In order better to expose the abdominal cavity, the rectus should be divided transversely beneath the skin just above the pubes, and the abdominal flaps may then be turned freely outward.

General Inspection of the Abdominal Cavity.—We first notice the position and general condition of the viscera. It is best at this stage of the examination to note the condition of the vermiform appendix, and to look over the peritoneal cavity for serum, inflammatory lesions, evidences of perforation, and for the existence of invagination, incarceration, and herniæ of the intestines. A small quantity of reddish serum is frequently found in the abdominal cavity, particularly in warm weather, as the result of commencing decomposition.

It should be remarked here that various striking changes in the character and appearance of the internal organs are produced by putrefaction—changes which are often mistakenly regarded as evidences of disease, and much experience is required in judging correctly of their significance. These changes are, in general, softening and discoloration, both of which may occur as the result of disease. It may be said in general that the post-mortem reddening, or hypostases, are most marked in the more dependent parts of the organs. Post-mortem softening usually affects entire organs, not being limited to a part, as is often the case in disease. Gray or grayish-brown post-mortem discolorations are apt to appear in those organs or parts of organs which lie in contact with the intestinal canal. Parts of internal organs, such as the liver, which have been the seat of localized congestion during life, may after death assume a dark greenish color.

The *omentum* is usually spread over the surface of the small intestines, but it may be rolled up and displaced in a variety of ways, or may be adherent at some point to the small intestines or to the abdominal wall.

The surface of the *small intestines* should be smooth and shining. They may be greatly distended with gas, and thus so completely cover the other abdominal viscera that it becomes necessary to let out some of the gas by a small puncture. The transverse colon passes across the abdomen through the upper part of the umbilical region. It may be lower than the umbilicus, or higher up against the liver and diaphragm; it may be distended with gas or contracted.

The *liver* is situated in the right hypochondriac and epigastric regions, filling the concavity of the diaphragm. Its upper border reaches, in the linea mammillaris, to the fifth intercostal space; in the linea axil-

laris, to the seventh intercostal space; close to the vertebral column, to the tenth intercostal space. At the median line the upper border of the liver corresponds to the lower border of the heart. The left lobe extends about three inches to the left of the median line. The lower border of the right lobe usually reaches to the free border of the ribs, while the left lobe is visible for about an inch below the ensiform cartilage. In women the liver is usually lower than in men.

The position of the liver is affected by changes in the thoracic cavity, forcing it downward; by changes in the abdominal cavity, forcing it upward; by constriction of the waist in tight lacing, forcing it either upward or downward; by changes in the size of the organ itself. The liver may not only be displaced downward, but dislocated so that its convex surface faces the abdominal wall and its posterior edge is turned upward against the diaphragm.

The *stomach* is situated in the left hypochondriac and epigastric regions, extending also into the right hypochondrium; it lies in part against the anterior wall of the abdomen, in part beneath the liver and diaphragm, and above the transverse colon. Its anterior surface, which is directed upward and forward, is in contact above with the diaphragm and the under surface of the liver, and lower down with the abdominal wall opposite to the epigastric region. Its posterior surface is turned downward and backward, and rests on the transverse mesocolon, the pancreas, and the great vessels. To its lesser curvature or upper border are attached the gastrophrenic ligament and the gastrohepatic omentum. To the greater curvature or lower border is attached the gastrocolic omentum. Its cardiac orifice communicates with the esophagus, its pyloric end with the duodenum.

When the stomach is distended the greater curvature is elevated and carried forward, the anterior surface is turned upward and the posterior surface downward. When distended with food or gas the organ is prominent; when empty it may hardly be visible below the ribs; when the intestines are dilated it may be entirely covered by them.

Before opening the thorax the hand should be passed up against the under surface of the diaphragm on either side, to determine its height. According to Quain, the vault of the diaphragm rises, in the dead body, on the right side to the level of the junction of the fifth rib and sternum, on the left side as high as the sixth rib. Both the relative and the absolute height of the diaphragm vary under a variety of pathological conditions.

If the existence of air or gas in the pleural cavities is suspected, the abdominal cavity should be filled with water and the diaphragm punctured below the level of the fluid. If air is present, it will escape in bubbles through the water.

The Thorax.

We now leave the abdominal viscera and proceed to the examination of the thorax. With a costotome or a strong knife the costal cartilages

are divided close to the ribs, the clavicles are disarticulated from the sternum, and the latter is removed, care being taken not to wound the large veins. We first examine the position of the heart and lungs.

The Heart.—The upper border of the heart is on a level with the third costal cartilage; the lower border extends from 1.3 cm. below the lower end of the sternum to the fifth left intercostal space. The left boundary of the heart is situated to the left of the junction of the fifth rib with its costal cartilage, and behind or to the left of a vertical line drawn downward from the left nipple. The right boundary extends 2.5 cm. to the right of the right edge of the sternum. The portion of the heart uncovered by the lungs is of an irregular quadrangular shape. Its lateral diameter is from 8.3 cm. to 11.1 cm.; its upper boundary varies from the level of the second costal cartilage to that of the fifth, but it is usually behind the third or fourth cartilage or fourth space.

The area of the heart which is found uncovered will, however, vary greatly, according to the degree to which the lungs collapse after the chest is opened. Any disease which diminishes the size of the lungs, or pleuritic adhesions which retract or bind them down, may increase the area of exposed heart. On the other hand, emphysema, pneumonia, or any disease which increases the size of, or retains the air in, the lungs, may diminish the area of exposed heart. The exposed area varies also with the size of the heart itself.

The pericardium is now opened by a slightly oblique incision on its anterior surface. The existence of serous, fibrinous, or purulent exudate, and of adhesions, is to be noted. A small quantity of clear serum exists normally in the pericardial sac, and this serum may be blood-stained from beginning decomposition. White thickenings of the pericardium on the surfaces of the heart are often seen; they do not indicate important disease.

Now that the pericardial sac is open, the position of the heart can be clearly seen. It lies obliquely in the chest, its long axis at an angle of about sixty degrees with that of the thorax. The portion of the heart which is first seen is the anterior surface of the right ventricle; upward and to the right of this is the right auricle, which lies about two-thirds on the right of the sternum and about one-third behind it. Its upper border usually corresponds to the plane of the middle of the anterior end of the second intercostal space on the right side. Its size varies with the amount of blood which it contains. The left auricle lies behind the root of the pulmonary artery, so that only its appendix is visible. The middle of the auricle corresponds to the third costal cartilage. Of the left ventricle only a narrow rim is seen, on the left side of the right ventricle. The pulmonary valve is usually entirely or in part on the left side of the sternum, behind the second space or third costal cartilage.

The aortic valve is usually at the level of the third cartilage or the third space, and behind the left two-thirds or half of the sternum. The mitral valve is oblique, the upper end to the left. It is on the level of the third to the fourth cartilage, near the middle of the sternum. The

tricuspid is oblique, its upper end to the left; the upper end is at the level of the third cartilage, the third space, or the fourth cartilage. The valve is opposite the middle of the sternum.

The hand should now be passed over the arch of the aorta, to ascertain whether or not an aneurysm is present. The heart is then grasped at the apex, raised out of the pericardium, tilted upward, and removed unopened by cutting through the great vessels at its base. It is advisable in many cases to remove with the heart the arch of the aorta and as much as is practicable of the associated great vessels. In some instances, for example when thrombosis of the pulmonary artery is suspected, it is well to remove the heart and lungs together.[1]

One may gain some knowledge of the sufficiency of the aortic and pulmonary valves if the heart is held horizontally by both auricles, so as not to pull the valves open, and water is poured into the aortic and pulmonary arteries. One observes how well the valves support the column of liquid. To ascertain the sufficiency of the mitral and tricuspid valves, the auricles are first laid open so as to expose the upper surfaces of the valves. A large pipe is passed through the aorta or pulmonary artery beyond their valves, and a small stream of water allowed to flow into the ventricles. The auriculoventricular valves will be swollen upward, and one may observe their degree of sufficiency. The tricuspid valve is normally somewhat insufficient. These water tests, however carefully applied, are not very reliable, since under the most favorable conditions the natural bearings of the valves are not perfectly preserved.

To ascertain the size of the different valvular openings, we introduce the fingers, held flat with their sides in contact, into each of the orifices, and then measure the width of the fingers at the point where they fill the orifice. In this way we find that, under normal conditions in the adult, the aortic valve measures about 2.5 cm., the mitral about 4.5 cm., the pulmonary about 3.1 cm., the tricuspid about 5 cm.

In order to examine *the interior of the heart*, one first makes an incision through the anterior wall of the *left ventricle* close by and parallel to the septum, and reaching to the apex of the ventricle (Fig. 824). Through this opening the blade of the enterotome is passed up into the aorta, the pulmonary artery being drawn aside with the fingers, and the ventricle and aorta are laid open (Fig. 825). With a little care the incision may be made to pass through one of the points of junction of the aortic valves.

The auricles and ventricles may be empty, or may contain fluid blood or the so-called *heart clots*. These heart clots are of two kinds—those which are formed some time before death, and those which are formed during the last hours of life and after death. The clots which are formed some time before death are usually associated with organic disease of the heart, especially with dilatation of the ventricles. They are firm, dry, and of whitish color, and may be infiltrated with the salts of lime. They lie free in the cavities of the heart, or entangled in the trabeculæ, or

[1] The opening of the heart in situ is recommended by many, but we are of the opinion that if care be exercised in the removal of the organ from the body and a sufficient portion of the great vessels at the base be included there is little risk of premature disturbance of thrombi, etc., on the valves, while the examination of the interior may be much more thoroughly, conveniently, and safely done.

firmly adherent to the endocardium, and are usually composed of coagulated fibrin, blood platelets, leucocytes, and red blood cells, and often lamellated. The clots which are formed during the last hours of life and after death are red, yellow, or white. They may be soft or succulent or quite firm, and may be free in the heart cavities, or be adherent

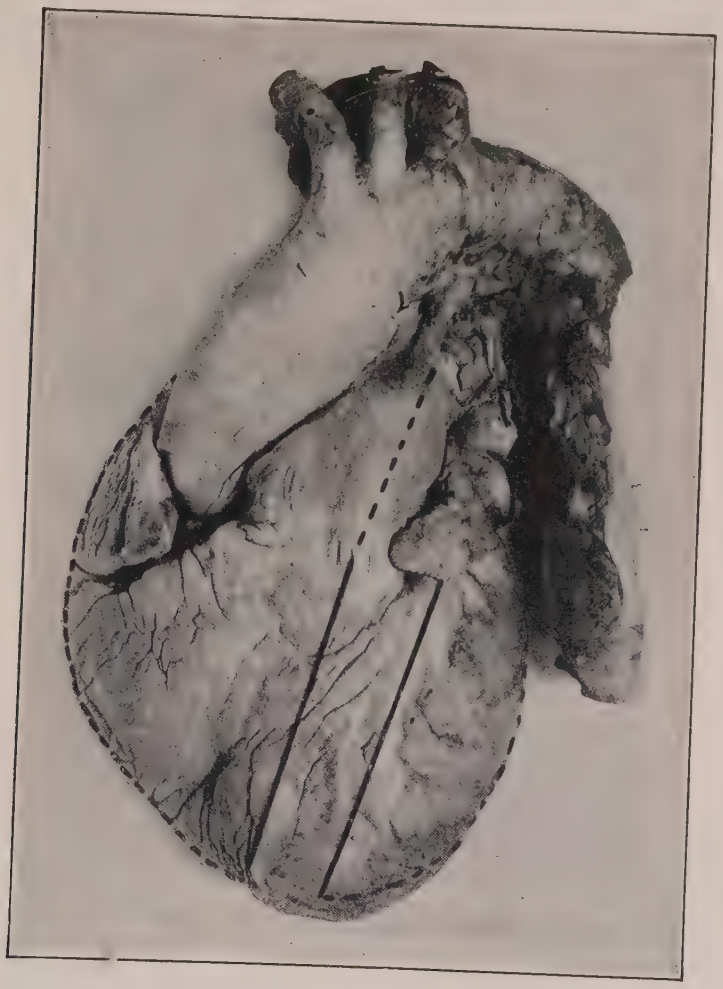


FIG. 824.—HEART SHOWING LINES FOR INCISION IN OPENING.

to the trabeculæ, or extend into the large vessels. They are usually most constant and of largest size in the right auricle and ventricle. Such clots may be formed within two hours after death. Clots of this character are common. If, then, the blood coagulates in the heart within twenty-four hours before death, this coagulum may not be distinguishable from the ordinary post-mortem clots. If it is supposed, therefore, that a person dies from heart clot developed a few hours before death,

the proof of this must be derived largely from the clinical symptoms, and not from the autopsy.

The condition of the aortic valves and of the endocardium, and the thickness and appearance of the walls of the left ventricle, papillary muscles, chordæ tendineæ, etc., are now noticed.

The *right ventricle* is now opened by an incision through its anterior wall, close to the septum (Fig. 824), and examined in the same way. The endocardium of the upper part of the left ventricle is sometimes

Fig. 825.—Heart Opened, Exposing the Aortic Valves.

thick and white, without the existence of valvular lesions or clinical history of disease. The endocardium and valves are often stained red, particularly in warm weather, by imbibition of coloring matter of the blood, set free by decomposition. This discoloration is especially marked in cases of infection with Bacillus aërogenes capsulatus.

To complete the examination of the cavities the enterotome is passed into each auricle, and carried down into the corresponding ventricle, and an incision made along the outer border of both auricle and ventricle to the apex of the latter. In this way the auriculoventricular valves are completely exposed. The coronary arteries should be opened through

all their main trunks, with fine probe-pointed scissors, and carefully examined for marks of inflammation, emboli, thrombi, etc.

In cases of Stokes-Adams disease or cardiac arrhythmias where injury of the conducting system of the heart is suspected, that organ should be opened according to the lines shown in the appended sketch (Fig. 826).[1] The superior vena cava should be cut high up, at least an inch from its auricular mouth, and as much as possible of the vessel should be spared in detaching the heart from the lungs on the right side. The vessels should then be tied, and the entire heart injected with 4 per cent. formal-

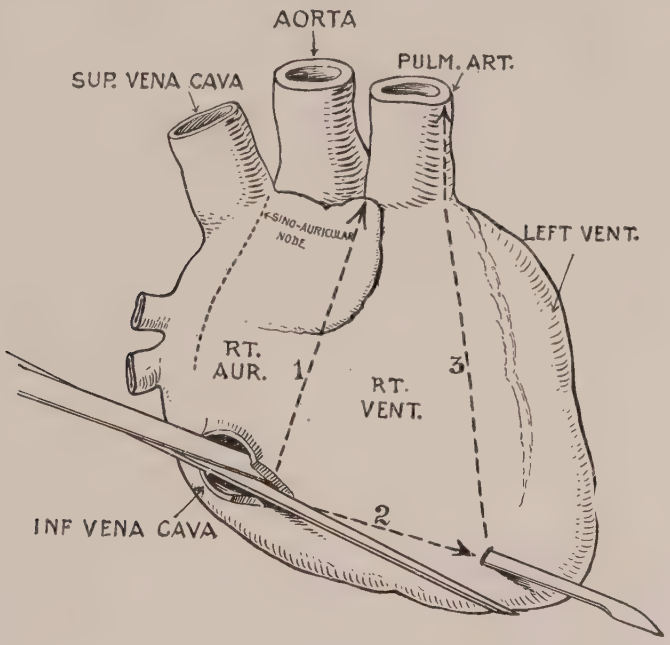


Fig. 826.—Special Incision for Opening Heart, in Order to avoid Injury to Conducting System.

dehyde, the organ being placed in a large quantity of the same fluid. The incisions should be made after the heart has hardened for two or three days; or, if preferred, the openings can be made while the heart is fresh and the fixation carried out on the opened organ. The first cut should be made with scissors along the opening of the inferior vena cava, the right auricular wall being cut parallel with and close to the auriculo-ventricular groove and the incision extended to the apex of the auricular appendix. This permits the inspection of the auricle and tricuspid valve. The scissors should then be inserted into the inferior vena cava and a cut made along the right border of the ventricle to its apex. A third incision should be made from the apex of the right ventricle up through the pulmonary artery, the scissors being kept well over to the left so as to pass between the left anterior and posterior cusps of the pulmonary valve.

[1] *Oppenheimer, B. S.*, Jour. Amer. Med. Assn., 1912, lix, 937.

The anterior papillary muscle should be avoided in this incision as the right branch of the auriculoventricular system passes directly from the interventricular septum to this muscle. On the left side an incision should be made through the orifices of the pulmonary veins, and then the left ventricle should be opened by a cut between the two papillary muscles to the apex; from the apex an incision into the artery parallel with the interventricular septum should be made. After formaldehyde fixation the heart should be hardened in 70 per cent. alcohol until suitable portions are embedded for cutting.

After removing the blood, the heart should be finally weighed. The normal average weight of the heart in adults is, according to an estimate of H. D. Arnold,[1] in males about 290 grams; in females about 260 grams.

The weight of the heart relative to that of the body is in males about 1 : 158 to 178; in females, about 1 : 149 to 176. According to Buhl, the average thickness of the wall of the left ventricle at about the middle of the cavity is from 1.6 cm. to 1.7 cm.; of the right ventricle, from 0.4 to 0.6 cm.

The size of the heart, speaking generally, corresponds to the size and the development of the individual. In judging of an increase or decrease in its size we must consider the weight of the organ and the thickness of its walls. If the person dies while the heart is contracted, the walls of the ventricles will appear thicker, their cavities smaller than usual.[2] If he dies of some exhausting disease like typhoid fever, or if decomposition has commenced, the heart walls will usually be flabby and the cavities will appear larger than usual.

Preservation of Specimens.—Parenchymatous and fatty degeneration of the heart may be studied microscopically by teasing the fresh muscle in 0.85 per cent. salt solution, or by examining in the same solution fresh sections made with the freezing microtome, or by hardening small pieces of the muscle in 1 per cent. osmic acid and teasing in equal parts of glycerin and water.

When lesions of the conducting system are to be studied the whole heart should be fixed for forty-eight hours in warm Orth's fluid or 4 per cent. formaldehyde. When the presence of bacteria is suspected, cultures should be made and the tissues should be preserved in strong alcohol.

The pleural cavities are next examined. The hand is passed into each, and the existence of serous or fibrinous exudation or of old adhesions ascertained. The method of detecting the presence of air has been given above. After the commencement of putrefaction reddish serum may accumulate in the pleural cavities. This should not be mistaken for the result of disease.

The Lungs.—Each lung is lifted up in turn, the vessels, etc., at its base are divided, and the organ is removed. If the pleura is very adherent it is better to strip off the costal pleura with the lung. After the external surface of the lung is inspected, and its size, shape, color, and consistence and the condition of the bronchial lymph-nodes are observed, the bronchi

[1] *Arnold*, Observations on the Weight of the Normal Heart in Adults, in Two Hundred and Sixteen Cases, Reports of the Boston City Hospital, 1899, x, 83.

[2] For method of determining hypertrophy of the heart, see *Müller, W.*, Die Massenverhältnisse des mensch. Herzens. 1883.

are opened with scissors having long, narrow, blunt-pointed blades, one blade a little longer than the other. The lung is held in the left hand with its base upward, the large bronchi which run on the inner side of the lower lobe being first opened, afterward those of the upper lobe. Each bronchus should be followed to its smaller ramifications.

We should observe the contents of the bronchi and the appearance of their walls. In the larger and medium-size bronchi the cartilages in their walls do not form complete rings, but appear shining through the mucous membrane like irregular white patches. This appearance should not be mistaken for a pathological change. In bodies which have been dead for some time, especially in cold weather, the bronchial mucous membrane may be red and swollen as a post-mortem change. The contents of the stomach are sometimes forced, after death, into the pharynx, and thence find their way into the trachea and bronchi, giving them a peculiar reddish and even gangrenous appearance. Bronchitis does not always leave lesions which can be seen after death. The large vessels should now be examined for thrombi, emboli, or other lesions.

After the examination of the bronchi the lung is turned over, the vessels, etc., at its root, are grasped with the left hand, and a long, deep incision is made from apex to base. We observe the appearance and texture of the lungs, whether the air vesicles are dilated (emphysematous) or filled with serum, blood, or inflammatory exudation. Fluid can be pressed out of the air vesicles without breaking down the lung tissue. Solid inflammatory exudation, on the other hand, renders the lung more resistant and easily broken down. Attention should be paid to the oozing of purulent or other fluid from the smaller bronchi when the lung is squeezed near the cut surface. It is the rule to find the lower lobes more congested than the upper.

Preservation of the Lungs and Bronchi.—If the lungs have been cut, small pieces from the affected portions of lung tissue or bronchi should be hardened in Orth's fluid, care being taken not to squeeze or handle them unnecessarily. It is better, when the microscopical examination is more important than the macroscopical, not to open the lungs at once, but to fill the air spaces with preservative fluid by means of a funnel attached to a short rubber tube and cannula, which is tied into the main bronchus. In this way not only are the minute structures better preserved, but the air vesicles are filled out and hardened in an approximately natural condition. Care should be taken not to have too great a pressure from the inflowing fluid, since then exudations might be displaced or the lung distorted or ruptured. While the lung is being filled it should be immersed in a vessel of the same preservative fluid, in which, after closing the cannula or ligating the bronchus, it lies for twenty-four hours. It is then cut into small pieces and the hardening completed. For the display of certain gross lesions, such as tuberculous and other cavities of the lungs and bronchi, tumors, etc., the lungs filled in this way are opened by an incision along the posterior surface from apex to base and hung in jars. For this purpose 4 per cent. formaldehyde solution may be used for both fixation and preservation in the jars. A variety of hardening agents may be used: Orth's fluid and 4 per cent. formaldehyde are on the whole the best. If, however, the lung is commencing to decay, strong alcohol will stop the process most quickly and give as good results as are possible under the circumstances. Alcohol should be used when the lungs are to be examined for bacteria.

It is often desirable, and particularly in cases in which the topography of lesions is to be studied, as in acute miliary tuberculosis, acute and chronic phthisis, infarctions, etc., to inject the blood-vessels with colored gelatin. The lung should, after the injection, be hardened in alcohol.

The Pharynx, Larynx, Esophagus, and Thyroid Gland.—For the removal of these parts the incision through the skin should be carried upward as far as practicable—when permissible, to a point 1 inch below the chin, the head being allowed to hang backward over the edge of the table.

The soft parts are dissected from the larynx, care being taken not to cut the thyroid body, and an incision is made through the floor of the mouth, following the internal surface of the inferior maxilla. Through this incision the fingers are introduced into the mouth, the tongue is drawn down, the posterior wall of the pharynx is divided above the tonsils, and the tongue, pharynx, and larynx are drawn out together. These organs are then pulled downward, and with the aid of the knife the trachea and esophagus are removed entire, the esophagus being cut just above the stomach. If the contents of the stomach are to be preserved, as in cases of suspected poisoning, a ligature is put around the esophagus just below the point at which it is to be cut off.

With the enterotome the pharynx and esophagus are now slit open upon their posterior surfaces. The mucous membrane thus exposed is examined for evidences of caustic poisons, of inflammation, tumors, strictures, varices, etc. The enterotome is next introduced into the larynx, and this organ and the trachea are laid open along the posterior wall. Here we look for edema of the arytenoepiglottidean folds (edema of the glottis), for evidences of catarrhal, croupous, ulcerative, and syphilitic inflammation, and for tumors and lesions of the laryngeal cartilages. Edema and redness of the larynx may result from post-mortem changes, especially in bodies which have been kept for several days in cold weather. A well-marked edema glottidis during life may leave no trace after death. Putrefactive changes usually commence early in the larynx and trachea.

The thyroid gland is dissected off and examined. Its weight varies considerably, being, according to Wegelin, 20 to 30 grams.

Preservation of the Pharynx, Larynx, Trachea, Etc.—These structures are freed from superfluous tissue and suspended entire by a thread in a large quantity of Orth's fluid or Flemming's osmic-acid mixture, after which the hardening is completed in the usual way. Four per cent. formaldehyde is now widely used. The esophagus should be stretched loosely on sheet cork with pins, and hardened in either of the above fluids. The thyroid may be cut into small pieces and similarly hardened.

The Abdomen.

Returning now to the abdominal cavity, we first dissect off the omentum. Tubercles of the peritoneum may be best seen in the omentum. The colon is then raised and dissected free, to the cecum on one side and to the rectum on the other. The colon and small intestines are then drawn first to the right and then to the left side, so as to expose in turn the right and left kidneys. As each kidney is brought into view an incision is made through the peritoneum over the track of the ureter. The ureter is followed through its entire length and its condition ascertained.

Sometimes one, more rarely all, of the abdominal viscera are un-

usually movable, owing to a relaxation of their ligamentous or other supports. This condition—enteroptosis—is common in the liver, more frequent in the spleen, and especially so in the kidneys. It has been occasionally described in the stomach and intestines.

The Kidneys.—These organs are now removed, the peritoneum and fat being separated from them with the hand, and the vessels being divided with the knife. The adrenals, at the upper end of each kidney, are removed at the same time. The kidneys may be softened by putrefaction, or the surface may have a greenish gray color, caused by the post-mortem action of putrefactive gases on the hemoglobin.

An incision is made through the capsule along the convex border of the kidney, and the membrane stripped off. We notice the degree of adherence of the capsule to the kidney, and also the surface of the latter, whether smooth or roughened, pale, congested, or mottled; an incision is made along the convex surface down to the pelvis, so that the organ is divided into halves. We observe the relative thickness of the cortical and pyramidal portions, as well as the size of the entire organ. To ascertain the latter point, it is well to weigh each kidney; the normal weight is from 130 to 150 grams The left kidney is, according to Orth, from five to seven grams heavier than the right. At from twenty to thirty-five years of age, according to Thoma, the weight of the heart is to the weight of both kidneys as 1 : 1.1. The weight of the kidneys of adults is given by Vierordt in general as about 0.48 per cent. of that of the entire body.

It is necessary to remember that in a kidney which is much atrophied there may be an increase of fat in the pelvis, which gives the organ nearly its normal size and weight, while the kidney tissue proper may have in great measure disappeared.

We now inspect the kidney tissue more closely, especially the cortical portion. The pyramids consist largely of tubes running in nearly straight lines from the apex to the base of each pyramid. These straight tubes pass from the pyramids into the cortex in bundles, called medullary rays, many of them retaining their straight course until they nearly reach the surface of the kidney. These straight tubules send off branches on all sides of the rays, which become convoluted, form Henle's loops, and finally terminate in the Malpighian bodies. In this way the cortex of the kidney, as seen in section, is divided into alternate bands of straight tubes, and convoluted tubes, with glomeruli; both sets of bands being perpendicular to the surface of the kidney, and called respectively medullary rays and labyrinths. About the convoluted tubules and glomeruli is a rich venous plexus; and since after death the blood usually remains in this plexus and in the glomeruli, the bands containing the convoluted tubules, *i.e.*, the labyrinths, usually appear red, while the medullary rays are grayish white. In a normal kidney, therefore, the cortex should be regularly striped in narrow alternating red and whitish bands. For a further description of the finer anatomy of the tubules, see page 865.

The average thickness of the cortex of the kidney is 4.8 mm.

If there be extensive congestion, the entire cortex is red. If the epi-

thelium of the tubules degenerates and fills them up, or if there are considerable changes in the interstitial tissue, the regular bands are lost and the cortex is irregularly mottled. If the tubular epithelium becomes filled with fat globules, this is indicated by an opaque yellow color of the affected parts; in many cases, therefore, the existence of a kidney lesion can be recognized with the naked eye.

If waxy degeneration be present to a marked extent, it may be manifest by a peculiar translucent appearance of the affected parts, but in most cases it is necessary to apply reagents to demonstrate it satisfactorily. The cut surface of the kidney is washed with water, to free it from blood, and repeatedly brushed with an aqueous solution of iodine (iodine 1 part, potassium iodide 3 parts, water 100 parts). The glomeruli and the blood-vessels are most frequently affected, and, if so, they may appear as mahogany-colored dots and lines on a yellow ground.

But this reaction is not constant, and, for accurate detection of amyloid substance, recourse should be had to other reagents applied to sections of the hardened tissues (see page 63).

The pelvis of the kidney should be examined for inflammatory lesions and calculi. Sometimes a whitish fluid is seen in the pelvis and can be squeezed from the papillæ; this is produced by a post-mortem desquamation of the epithelium, but is likely to be mistaken for pus.

Preservation of the Kidney.—If the kidney is not opened, the blood-vessels may be injected through the renal artery, slowly and under a low pressure, with Orth's fluid or Flemming's osmic-acid mixture. After the vessels are filled with either of the above fluids, they are tied, and the entire organ is placed in a large quantity of the injecting fluid for twenty-four hours. The kidney is then cut into small pieces, and the hardening is completed in the usual way.

In most cases, however, the kidneys will have been opened for inspection at the autopsy. Then small pieces are removed from the various regions and hardened in one of the above fluids or in 4 per cent. formaldehyde.

Kidneys which are to be examined for the presence of bacteria should be cut into small pieces and placed at once in strong alcohol, which should be changed once or twice; in this they are permanently preserved.

The Adrenals—Suprarenal Capsules.—These are, in the fetus, of an ovoidal, in the adult, of a triangular shape. They are situated at the upper and inner border of the kidney, to which they are loosely attached by connective tissue. On the anterior surface is an irregular fissure, called the hilus, from which the veins emerge. The size of the adrenals varies considerably, but in the adult the average vertical diameter is from 3.2 cm. to 4.5 cm., the transverse diameter about 3.2 cm., and they are from 4.2 mm. to 6.4 mm. in thickness. They weigh in the adult from 4 to 8 grams. They are relatively larger in children than in adults. They are composed of a cortical and a medullary portion, the cortex forming a yellowish shell around the dark red or brown medulla. They are enclosed in a connective-tissue capsule, from which fibrous processes extend inward, dividing the gland into a series of irregular chambers. Those in the cortex are mostly elongated, giving this portion a striated appearance, while those in the medulla are polyhedral. It is in these spaces that the parenchyma cells lie. The adrenals readily decompose; the inner layer of the cortex may soften and break down, so that the outer

zone forms a sort of cyst filled with reddish brown broken-down substance. Hypertrophy, tuberculosis, and cheesy degeneration, fatty degeneration, and tumors are to be looked for.

PRESERVATION.—The adrenals should be hardened in Orth's fluid or in strong alcohol. Four per cent. formaldehyde is also useful, especially if frozen sections are to be made for study of anisotropic fats.

The Spleen.—This organ has, when removed from the body, the general shape of a flattened ellipsoid, most curved on its external and posterior surface. It is situated in an oblique position on the left side of the stomach, and between its cardiac end and the diaphragm. The vessels are given off from its inner surface, which is crossed by a more or less well-marked vertical ridge. The point of emergence of the vessels is called the hilus. Its long diameter extends from the seventh intercostal space to the eleventh rib. Its upper portion is separated from the ribs by the lungs; its lower portion, by the diaphragm.

It is, according to Vierordt, on the average, from 12 to 13 cm. long; from 7 to 8 cm. broad, and about 3 cm. thick. Its average weight is about 171 grams. The dimensions of the spleen as given by Krause are somewhat greater than the above; but its measurement and weight vary considerably within the limits of health. It is in these respects the most variable organ in the body. In old age the average weight gradually diminishes.

The spleen is inclosed in a fibrous capsule covered with peritoneum. The parenchyma is formed of blood-vessels and fibrillar connective tissue, and of a soft, dark red pulp in which are embedded whitish spheroidal or elongated bodies, the glomeruli, or Malpighian bodies. In the normal human spleen the glomeruli are usually hardly perceptible to the naked eye, but sometimes they are very plain. Sometimes the fibrous stroma is very apparent, sometimes not.

The size, consistence, and color of the organ vary a good deal within normal limits; it may soften in decomposition. Thickenings of the capsule and abnormal adhesions are very common, and often occur without any clinical history indicating disease. We should look for changes in size, color, and hardness; for pigmentation, hyperplasia of the connective tissue, amyloid degeneration, tubercles, and infarctions.

Not infrequently one or more spheroidal or flattened so-called accessory spleens are found in the vicinity of the spleen; they vary in size from that of a pea to that of a walnut.

PRESERVATION.—In certain diseases of the pulp, anemia, leukemia, malaria, etc., smears or impressions of the tissue should be made, and examined by the staining methods described under the lesions of the blood. For general purposes small pieces of the organ are hardened in Orth's fluid, in Flemming's osmic-acid mixture, or in alcohol. Helly's fluid or carefully neutralized 4 per cent. formaldehyde are employed for finer cytological studies.

The Intestines.—The rectum is divided, the intestine is seized with the left hand, and, being kept stretched, is separated from its attachments by repeated incisions through the mesentery close to the gut, until the duodenum is reached, where the intestine is again cut off. The operation

is more cleanly if, before dividing the gut, ligatures are placed around it at either end. The entire length of the gut is now laid open with the enterotome along the mesenteric attachment; the mucous membrane is cleaned with a stream of water and then examined.

In cases of suspected poisoning, a ligature should be placed around the rectal end of the gut and two around the duodenal end, and it should then be cut off below the former and between the latter ligatures. The gut is now opened and the contents are emptied into a clean glass jar for delivery to the chemist, care being taken that they are not allowed to touch anything but the inner surface of the jar. After washing the intestine in pure, fresh water and examining it, it should be placed entire in another clean jar and the jar sealed.

Cadaveric lividities are very common in the intestines, and are usually most marked in the dependent portions. They are apt to occur in patches, but may be diffuse and very extensive. If the wall of the gut be stretched, they are often seen to be discontinuous, owing to the pressure of the blood from the parts which are squeezed by folds. Small patches of arborescent or diffuse red staining are often seen, formed by the imbibition from the vessels of decomposing hemoglobin. In the more advanced stages of decomposition the mucosa may be softened and loosened. A dark purple or brownish discoloration of the entire intestinal wall is frequently seen, either diffuse or in patches. Much experience and careful observation are requisite in forming a correct judgment regarding the significance of changes of color in the intestines. Caution is necessary in distinguishing normal digestive hyperemia from abnormal congestion. A very considerable congestion may exist without disease.

The lesions ordinarily to be looked for are catarrhal, croupous, and ulcerative inflammations, perforations, hemorrhages, strictures, tumors, amyloid degeneration, swelling and ulceration of the solitary follicles and Peyer's patches, and pigmentation. For the detection of amyloid degeneration of the mucosa this structure should be carefully washed, and brushed with a solution of iodine.

Preservation.—For the general purposes of microscopic study, portions of the gut should be gently stretched on cork (the mucosa side free) and hardened in Orth's fluid or in Flemming's osmic-acid mixture.

For obvious reasons the mucous membrane should be handled as little as possible, for, in the majority of cases, decomposition and softening have already set in at the time of the autopsy, and, even under the most favorable conditions, the epithelium is very easily rubbed off.

In cases in which the most perfect preservation of the topographical features, as well as the minute structure of the intestinal mucosa, is desired, even at the expense of an inspection of the fresh tissue, another mode of procedure is to be recommended. Selected segments of the gut are, after removal from the body, allowed to remain unopened on the table while ligatures are tied around the ends. The isolated segments, or the whole gut, may now be moderately filled—not distended—with one of the above fluids by means of a syringe with a needle cannula; or one end of the segment may be tied and the fixative introduced through a funnel at the other, which end is then ligated. The segments to be preserved should now be placed unopened in the fixative solution. After twenty-four hours they may be opened with scissors or a sharp knife, cut into suitable pieces, and kept permanently in 80 per cent. alcohol.

The Stomach and Duodenum.—We now introduce the enterotome into the duodenum at its transverse portion, and open it on the convex border.

When the pylorus is reached the incision is carried obliquely over to the greater curvature of the stomach, along which it is extended as far as the esophageal opening, and the organ examined in situ; or, if a more careful examination of the stomach is called for, after ascertaining whether or not the bile duct is pervious (see below), the duodenum and stomach may be removed together, and the stomach opened and examined on the table. Alterations in size and form, the presence of tumors, ulcers, etc., may now be sought for.

If poisoning be suspected, a ligature should have been placed, earlier in the examination (see above), around the lower end of the esophagus and the duodenum. The stomach and duodenum are now removed together unopened. They are to be opened in a carefully cleansed glass jar, and after an inspection of the mucous membrane and the contents with the naked eye and a hand lens, stomach, duodenum, and contents are to be sealed in the jar for the chemist.

We now look for the orifice of the bile-duct, which will be found about the middle of the descending portion of the duodenum on its concave border. Pressure on the gall-bladder or on the common duct will usually cause the bile to flow into the intestine if the ducts are pervious. But a sufficient degree of stoppage may exist in the ducts to give rise to marked symptoms of disease, without preventing the flow of bile under these conditions, even with a moderate pressure. A long director is now passed into the gall-duct, which is laid completely open; ulcerations, cicatrices, gall-stones, inflammatory lesions, and tumors are looked for. In stricture of the gall-duct the mucous membrane above will often be found bile-stained, while below it is colorless. At this point, should there be any special reason for doing so, the portal vein, which lies close behind the ductus choledochus, should be opened and examined for periphlebitis, phlebitis, and thrombosis. The mucous membranes of the duodenum and stomach are now examined. Acute inflammation from caustic poisons, chronic catarrhal inflammations, hemorrhages, ulcers, erosions, swelling of the solitary follicles (lymph-nodules), and tumors are lesions most frequently seen. We sometimes find a diffuse congestion of the stomach, similar to that produced by irritant poisons, as a result of doses of croton oil given just before death.

Preservation.—The same methods should be used as for the intestines (see above). Tumors should be cut into small pieces and hardened in Orth's fluid or 4 per cent. formaldehyde.

The Liver.—To remove the liver, the diaphragm is first divided on one side of the suspensory ligament as far back as the spine; the suspensory ligament is then divided; then the right and left lobes being in turn raised, the lateral ligaments are severed. Then, the left lobe being seized, the organ is dragged obliquely downward into the abdominal cavity, the remaining attachments being dissected away. The liver is first laid on its superior surface and the gall-bladder and its contents are examined. The character of the gall is to be determined, and gall-stones, inflammatory lesions, and tumors are to be sought for. To determine the actual size of the organ, it should be both measured and weighed. Its

size varies greatly in different healthy individuals, but in general it may be said that it measures from 25 to 30 cm. transversely, from 15.3 to 18 cm. anteroposteriorly, and from 9 to 12 cm. at its thickest part; its ordinary weight is between 1,550 and 1,860 grams. In children its weight relative to that of the body is greater than in adults. The liver is increased in size and weight during digestion and by congestion from any cause.

The convex surface of the right lobe of the liver not infrequently shows several grooves running from front to back, approximately parallel with the suspensory ligament of the liver. These grooves, which may be found in persons of all ages, are believed by some to be usually congenital, by others to be the result of pressure of the diaphragm and the abdominal muscles on a relaxed atrophic liver. They seem in any event to be of no practical importance. On the other hand, a transverse groove running at right angles to the axis of the body is a not infrequent result of tight lacing, and is usually associated with local connective-tissue thickening of the capsule and underlying tissue of the liver. In this way the liver may become much distorted and the gall-bladder compromised.

The capsule of the liver is now examined; the organ is then laid on its lower surface and several deep incisions are made from above downward. The color and consistence of the liver tissue should be noticed, also the distinctness with which the lobular outlines can be seen; whether or not the centers of the lobules are congested or their peripheries lighter in color than usual; the presence of tumors, tubercles, abscesses, ecchinococcus, new connective tissue, and pigmentation. Suspected amyloid degeneration should be tested for by iodine solution.

We often find the surface of the liver of a greenish or very dark brown color; less frequently the same color extends into the substance of the organ. This discoloration, which is entirely post-mortem, is, like the similar discoloration of other internal organs, produced by the action of the gases of putrefaction on the coloring matter of the blood.

Preservation.—For the study of parenchymatous degeneration, sections of the fresh frozen tissue or small teased fragments should be examined in 0.85 per cent. salt solution. For general purposes small pieces should be hardened in Orth's fluid, in 4 per cent. formaldehyde, or in alcohol. Tumors should be treated in the same way.

The Pancreas.—This organ, of a light yellowish red color, is elongated, irregularly prismatic in shape, and flattened anteroposteriorly; the right end, called the head, is broader than the rest and lies in the concavity of the duodenum. The remainder of the organ, the body and tail, are usually tapering and lie transversely in the abdominal cavity, the tail reaching to the spleen. Its size and weight vary considerably; its usual length is from 15.3 to 23 cm.; its breadth about 3.8 to 4.5 cm.; its thickness about 1.3 to 3.8 cm.; its weight is usually from 70 to 108 grams. The organ may be rounded instead of flattened; the head and tail may be disproportionately large; the tail may be unusually long or may be divided or curved. The superior mesenteric artery and vein,

which pass behind the gland, are usually partly embedded in it, but are sometimes completely inclosed.

A longitudinal incision should be made through the whole gland, and its substance and duct should be searched for calculi, tumors, malformations, and evidences of acute and chronic inflammation, fat necrosis, and amyloid degeneration of the blood-vessels. The pancreas is frequently of a dark red color from post-mortem staining.

Preservation.—Portions of this organ should be hardened in strong alcohol, Orth's fluid, or Flemming's osmic-acid mixture.

The examination of the **thoracic duct,** which lies to the right and posterior to the aorta, may now be made. Among the most important of its lesions is tuberculosis, since it has been shown that from a tuberculous lesion here the generalization of bacilli not infrequently occurs. Inflammatory lesions, carcinoma, and partial or total occlusion from pressure may be found.

The **solar plexus,** which surrounds the origin of the celiac axis and the superior mesenteric artery and lies between the adrenals, may now be sought. Lesions of the *semilunar* and other *ganglia* are to be noted—atrophy, pigmentation, and degenerations.

The condition of the hemolymph-nodes in the prevertebral fat should be ascertained (see page 552).

The Aorta.—The size of the lumen of this vessel should be determined. The average circumference of the ascending aorta in the adult may be taken in general as about 69 mm.[1] Either in situ or after removal the aorta should be opened by an incision extending its whole length and continued into its larger branches.

The Genitourinary Organs.

The Male Organs.—If the urine is to be examined it may be drawn off with a catheter; or a vertical incision may be made into the bladder just above the symphysis pubis, and some of the urine dipped out. The cut end of the rectum should now be grasped with the left hand and raised up, and this and the bladder, prostate gland, etc., dissected away from the pelvis, the knife being carried close to the bone. The bladder is now drawn backward and the loose tissue close under the symphysis pubis cut. The body of the penis is then shoved backward within the skin and dissected away from behind, beneath the symphysis, and finally cut off just behind the glans penis. The penis and bladder are now drawn backward and upward, and the pelvic organs removed together. Or, the penis may be removed by sawing away the bones above the pubic arch, and then dissecting away the penis, whose root is thus exposed.

The pelvic organs are then laid on the table, the bladder uppermost; a long director is passed into the urethra, which is opened on its upper surface through its entire length, and the bladder widely opened. In the *urethra* the presence of strictures, diverticula, ulcers, inflammatory

[1] See Vierordt's Tables; also *v. Ritoók*, Ztschr. f. klin. Med., 1907, lxi, 36.

lesions, is to be noticed; in the *bladder* inflammatory lesions, hypertrophies, congestion and ecchymosis of the mucous membrane, hyperplasia and ulcers of the lymph-nodules, and tumors. The organs are now turned over; the *rectum* is opened and examined for varicose veins, hemorrhages, ulcers, strictures, and tumors. The *prostate gland* is then cut into and the presence of calculi, inflammatory lesions, hypertrophies, and tumors sought for. Lastly, the *vesiculæ seminales* are examined, in which, though rarely, we may find evidences of tuberculous inflammation and dilatation.

The testicles may be removed, when necessary, without cutting the scrotum, by enlarging the inguinal canals from within and crowding the glands through them and cutting them off. The average weight of the adult testicle with its epididymis is, according to Krause, from 15 to 24.5 grams. Inflammatory lesions, tuberculosis, abscesses, and tumors are the most frequent lesions.

Preservation.—The urethral canal and bladder may be pinned open and hardened in Orth's fluid or in Flemming's osmic-acid mixture. The prostate, vesiculæ seminales, testicles, and tumors may be hardened in the same fluids or formaldehyde.

The Female Organs.—The position and general condition of the pelvic organs should first be determined by inspection. Abnormal adhesions of the ovaries, broad ligaments, Fallopian tubes, and uterus; malpositions of the uterus; subserous tumors of the uterus, and ovarian tumors, are frequently observed. Hemorrhage into the posterior *cul-de-sac* is sometimes found. The urine should be collected, if necessary, as above directed; the organs should be dissected away laterally, as in the male, care being taken not to injure the ovaries and Fallopian tubes. The bladder is then drawn strongly backward and upward, and dissected away from the symphysis and the pubic arch, and, the point of the knife being carried forward and downward, the vagina is cut off in its lower third, the rectum severed just above the anus, the remaining attachments cut, and the pelvic organs are taken out together. If it is necessary to remove the external generative organs, after freeing the lateral surfaces of the internal organs and the bladder, the legs are widely separated and the vulva and anus circumscribed by a deep incision. The tissues close beneath the pubic arch are now dissected away from below, and the vulva is thrust back beneath the symphysis; it is now seized above the bone, and together with the anus dissected away and removed with the other organs.

The bladder is first opened and examined. The *vulva* may now be examined for hypertrophies, inflammatory lesions, ulcers, cicatrices, cysts, and tumors. The *vagina* is opened along the anterior surface; its more common lesions are inflammations, fistulæ, ulcers, tumors, and rarely cysts.

The Uterus.—Before opening this organ its size and shape should be determined. The adult virgin uterus is a pear-shaped body, flattened anteroposteriorly; the upper portion, or body, is directed upward and forward, while the lower portion, the cervix, is directed downward and backward. It is covered anteriorly by peritoneum to a point a little

below the level of the os internum; posteriorly, to a point a little below the level of its junction with the vagina. The peritoneal investment separates from the organ at the sides to form the broad ligaments. The uterus is held in position by the broad and round ligaments and by its attachments to the bladder and rectum and vagina. The upper end, the fundus, does not extend above the level of the brim of the pelvis. Its average length is about 7.6 cm.; its breadth about 5.1 cm.; its thickness about 2.5 cm.; its average weight is about 31 to 46 grams. During menstruation the uterus is slightly enlarged, the mucous membrane of the body becomes thicker, softer, and its vessels are engorged with blood; while its inner surface is more or less thickly covered with blood and cell detritus. A description of the complicated changes in the uterus which pregnancy entails may be found in the works on obstetrics. After pregnancy the uterus does not return to its original size, but remains somewhat larger; the os is wider and frequently fissured.

We not infrequently find in the mucous membrane of the lower part of the cervix small, transparent, spheroidal structures, called ovula Nabothi; these are small retention cysts caused by the closure of the orifices of the mucous glands. The more common lesions observed in the uterus are malpositions, malformations, lacerations, ulcerations of the cervix, acute and chronic inflammation of the mucous membrane or muscularis, or both, thrombosis and inflammation of the veins, and tumors.

In the infant the uterus is small, the body flattened, the cervix disproportionately large. During childhood the organ increases in size, but the body remains small in proportion to the cervix. At puberty, the shape changes, and the body becomes larger.

The ovaries are flattened, ovoidal bodies, situated one on each side, and lying nearly horizontally at the back of the broad ligament of the uterus. Their size is variable, and they are usually largest in the virgin state. They measure about 3.8 cm. in length, 1.9 cm. in breadth, and nearly 1.3 cm. in thickness. Their average weight is from 3.9 to 6.5 grams. The sides of the ovary and its posterior border are free; it is attached along the anterior border; to its end is attached the ovarian ligament, to its outer extremity one of the fimbriæ of the Fallopian tube. The ovary is covered on its free surface by cylindrical epithelium, and its surface is less glistening than the general peritoneum. The surface of the ovary is smooth in the young, but becomes rougher and depressed in spots as the process of ovulation goes on. In adult females we usually find corpora lutea in their various stages. We should seek for evidences of acute and chronic inflammation, for tumors and cysts.

The Fallopian tubes, lying in the upper margin of the broad ligaments, are from 7.6 to 10 cm. in length. The length often differs considerably on the two sides. They commence at the upper angles of the uterus as small perforated cords, which become larger farther outward, and bend backward and downward toward the ovary. They terminate in an expanded fimbriated extremity about 2.5 cm. beyond the ovary. They are covered by peritoneum, and the mucous membrane lining

them, continuous with that of the uterus, is thrown into longitudinal folds. Malpositions by adhesions, closure, inflammations, and cysts are the more common lesions. The possibility of tubal pregnancy should be borne in mind.

PRESERVATION.—All of these organs and their tumors may be hardened in Orth's fluid or in 4 per cent. formaldehyde. The vagina should be stretched flat on cork, and the cavity of the uterus laid wide open. Great care should be taken not to touch either the internal surface of the uterus or the external surfaces of the ovaries, since in both the epithelium is very easily rubbed off.

It is better, after opening them by a transverse incision, to suspend the ovaries by a thread in a jar of the preservative fluid than to let them lie on the bottom, since the epithelium is thus less likely to be rubbed off. Larger cysts of the ovary for exhibition purposes should be distended with preservative fluid.

The Closure of the Body after the Post-mortem Examination.

At the end of the autopsy the body should be restored as nearly as possible to its natural external appearance.

Fluids should be removed, vacant spaces filled with absorbent material, such as cotton, jute, or sawdust, and the incisions closed by sutures.

Bacterial Examination of Post-mortem Specimens.

It is often important to make a thorough post-mortem examination by cultures as well as morphologically of the blood and of all the viscera. This is important not only in those cases which during life gave clinical evidence of general infection, but also in many forms of disease whose nature is still wholly obscure.

In the interpretation of the result of all such examinations, however, it should be borne in mind that after death a new distribution of germs may occur, and that from the gastrointestinal canal and from other surfaces or cavities of the body microorganisms may, as decomposition progresses, penetrate the tissues and the viscera.

A careful consideration of the general conditions under which the body has been kept and its state of decomposition is of special importance in the interpretation of the significance of the Bacillus coli communis, which is always present in such enormous numbers in the intestinal canal, and which is not only apt to effect wide distribution in the body after death, but as a result of careless manipulation is likely to be accidentally brought in contact with other viscera after the opening of the gut. The preparation of cover-slips for staining and the making of cultures is, as a rule, best done at the autopsy table.

It is well as each organ is exposed—commencing with the heart—to sear the surface of the organ to be examined with a broad-bladed knife heated over a flame, and then, making an incision through the seared surface with a sterilized scalpel, to press a sterilized cotton swab into the opening and absorb the juices which exude, or to pick out a small fragment of the solid tissue from the depths of the opening, or to secure some of the blood or fluid on a sterilized platinum loop; and then with the material thus procured to make the required cultures and afterward the cover-slip smears for staining.

If it be necessary to transport the material to the laboratory before making cultures, it is well to reserve the unopened organs, or large portions of these in the case of the solid viscera, and to wrap each separately in a cloth saturated with sublimate solution, or to put each in a separate sterile receptacle for transportation.

It is well to remember that in the last hours of life the safeguards of the body against the entrance and growth of microorganisms may be ineffective, so that the determination of the significance of bacteria in the tissues a short time after death requires care and experience.[1]

Autopsies in Medicolegal Cases.

While every autopsy should be made as carefully and completely as circumstances permit, it should be always borne in mind that in examinations which may have medicolegal bearings it is of the highest importance to examine thoroughly both macroscopically and microscopically every part of the body from which light may be derived as to the cause of death, for in medicolegal cases it is not infrequently as important to be able by a complete examination to declare the absence of lesions which could cause death, as to determine the presence of those upon which the opinion as to the actual cause of death in a particular case rests. Bearing this in mind, the technique of autopsy-making is essentially the same whatever the ends which the facts elicited may be destined to serve.

Autopsies in Cases of Suspected Poisoning.

In cases of suspected poisoning which may possibly have a medicolegal bearing, the examination should be made with extreme care and thoroughness. The inspection of the body and the examination of *all* the viscera should be thorough and detailed. Every appearance should be noted at the time, and nothing left to the memory. It is well to have an assistant record the observations as they are made. The disposition of the parts and organs in jars should be also noted at the same time.

It is important to remember that many poisons destroy life without producing appreciable lesions, and also that many cases of sudden death occur, not due to poisons, and without any discoverable cause.

In bodies which are exhumed for examination, the tissues may be so changed by decomposition that it is impossible to say whether lesions have or have not existed. In such cases the careful and separate preservation of the viscera and other parts for chemical examination, is often all that can be done.

It is always best, in cases of suspected poisoning, to preserve for the chemist not only the stomach and intestines, but the entire liver and brain; or, if only portions of these can be saved, these portions should be carefully weighed, as well as the entire organs, and the relative amount of tissue reserved carefully noted at the time. It is even well, particularly in cases in which the administration of the readily diffusible

[1] For details of bacterial flora of the human body see pp. 181 and 232.

poisons, such as arsenic, strychnia, etc., is suspected, to preserve the whole of all the internal organs, together with a large piece of muscle and bone; since with large quantities of tissue the results of the chemical analysis depend less upon calculations, and are hence more comprehensible to the average jury. In all such cases jars should, if possible, be procured which have never been used before, and these should be carefully washed and rinsed with distilled water. They should have glass stoppers and be sealed at once and carefully labelled before leaving the hands of the operator. If they can be delivered to the chemist without much delay, no preservative fluid should be added. If they are to be kept for a considerable time, pending the action of a coroner's jury or for some other reason, a small quantity of pure strong alcohol may be poured over them. The operator should be particular to preserve a quantity, at least half a pint, of the specimen of alcohol used, in a clean, sealed, and labelled bottle, so that this may be tested by the chemist and be proved to be free from the poison. It is better in all cases, however, to avoid, if possible, the use of alcohol. In all autopsies which may have medicolegal importance full notes should be taken by an assistant as the operation proceeds, carefully read over immediately afterward and dated, and kept by the operator for future reference. The labelling and disposition of the jars should be recorded in the notes. The specimens should not for a moment be out of the sight of the operator until they are placed under lock and key and seal, or are delivered to some authorized person, so that there may be no question of their identity should the case come into court.

Examination of the Bodies of New-born Children.[1]

In examining the bodies of new-born children, we may have to determine, besides the ordinary lesions of disease, the age of the child, whether it was born alive, how long it has been dead, what was the cause of death.

Size, Age, and Characters of the New-born Child.—The fresh corpse of a new-born child at term no longer resembles that of the immature fetus. The skin is firm and pale, like that of an adult. The lanugo has disappeared except on the shoulders. In the majority of cases the hair on the head is 1.5 to 2 cm. long. The great fontanelle is, on the average, 2 to 3 cm. long. As determined by an analysis of 661 cases, the average length is 50 cm., the weight 3,256 grams. The nails are hard and reach to the tips of the fingers, but not to those of the toes. The cartilages of the ears and nose are hard. The labia are more nearly closed. An ossification center in the lower epiphysis of the femur should be sought for, as its presence is one of the most reliable signs of the maturity of the fetus. If it is absent, the fetus is, as a rule, not more than thirty-seven weeks old; but in rare cases it may be absent at term. A center of ossification 1 mm. in diameter indicates an age of thirty-seven to thirty-eight weeks, if the child was born dead or died soon after birth. Rarely it is no larger than this at term. A diameter, at birth, of 1.5 to 9 mm. indicates an age of 40 weeks. A diameter of more than 9 mm. indicates, as a rule, that the child has lived some time after its birth; a less diameter than 7 mm., however, does not prove the contrary.

Twenty-four hours after the birth of the child the skin is firmer and paler. The umbilical cord is somewhat shrivelled, although still soft and bluish in color. From

[1] The human embryo, according to the estimate of *His*, measures in length approximately at 4 weeks from 7–8 mm.; at 5 weeks 13 mm.; at the end of the second month 25–28 mm. *Schröder* estimates the approximate length of the fetus at later lunar months as follows: 3d, 70–90 mm.; 4th, 100–170 mm.; 5th, 180–270 mm.; 6th, 280–340 mm.; 7th, 350–380 mm.; 8th, 425 mm.; 9th, 467 mm.; 10th, 490–500 mm. Consult for further data *McMurrich*, The Development of the Human Body, 1903, p. 108 (bibl.), and *Keibel* and *Mall*. Manual of Human Embryology, Philadelphia, 1910.

the *second to the third day* the skin has a yellowish tinge and the cuticle sometimes appears cracked. The umbilical cord is brown and dry. From the *third to the fourth day* the skin is yellower, and the cuticle is apt to separate from the skin. The umbilical cord is of a brownish red color, flattened, semi-transparent, and twisted. The skin around its insertion is red and congested.

General Inspection.—The *head* should be examined for the marks of injuries. Very commonly some portion of the scalp will be found swollen and infiltrated with blood and serum. This may be the *caput succedaneum* formed during delivery. The mouth and nose should be examined for the presence of foreign bodies which might have caused suffocation.

The *neck* should be examined for marks of strangulation. The umbilical cord may be twisted around the child's neck and strangle it. The mark left by the cord is usually continuous, broad, not excoriated, sometimes accompanied by ecchymoses in the skin.

The surface of the body should be examined for the presence of vernix caseosa, blood, marks of injury, and the existence of putrefaction. It should be remembered that putrefaction is apt to commence earlier in the bodies of young children than in those of adults.

The umbilical cord may be cut or torn. It usually separates by the fifth day, sometimes not until the tenth. If the umbilicus is cicatrized and healed, the child has probably lived for three weeks. A zone of redness around the insertion of the cord may exist previous to birth. Redness and swelling (which may disappear after death) with suppuration can be found only in a child which has lived for several days. The drying and mummification of the cord may take place as well in dead as in living children. It is possible for a child to die by hemorrhage from a cut or torn cord, either before or after it has breathed. The umbilical vessels should be examined, as they may be the seat of umbilical infection.

The *extremities* may exhibit fracture of the bones. These may occur during intrauterine life from injuries to the mother or from unknown causes; or may be produced by violence in delivery, or by injuries after birth.

Internal Examination.—*The Head.*—The fontanelles and sutures should first be examined as to their size and for penetrating wounds. An incision should then be made through the scalp across the vertex, and the flaps turned backward and forward as in the adult. With a small knife the edges of the bones should be separated from the membranous sutures and the dura mater, beginning low down in the frontal and going back into the lambdoidal suture on either side. The bones are then drawn outward and cut through around the skull with strong scissors. The brain is removed and examined as in the adult.[1]

Effusions of blood—cephalhematoma—may be formed, soon after birth, between the pericranium and bone, or, more rarely, between the dura and bone. Clots are also found between the dura mater and skull; between the dura and pia mater; more rarely in the substance of the brain, as the result of protracted or instrumental deliveries, or of injuries after birth.

The cranial bones may be malformed, or exhibit the lesions of rickets or caries, or be indented, fissured, or fractured. These latter lesions may be produced during intrauterine life by injuries to the mother, by unknown agencies, by difficult deliveries, or by direct violence after birth.

In cases of chronic internal hydrocephalus in young children, in which the ventricles are much dilated and the brain substance is thinned over the vertex, the brain is very apt to be torn in removal, and the amount of dilatation thus becomes difficult of determination. It is, therefore, better in such cases to place a pail of water beneath the head, or even immerse the latter in it, and remove the brain in the water. In this way it floats after removal, supported on all sides. It may now be opened in the water and the extent of the lesion determined at once, and parts saved for microscopical examination.

If it be desired to preserve the brain for demonstration of the lesion or for a museum specimen, it should be transferred unopened to a large jar containing 4 per cent. formaldehyde. A portion of the ventricular fluid should now be removed with

[1] Or an incision through the bones with a fine saw may be made as in the adult.

a syringe provided with a small cannula, and replaced by formaldehyde. This may be done by puncturing the ventricles from below. The fluid in the jar, as well as in the ventricles, should be changed in forty-eight hours. The brain may then be cut transversely across, when the degree of dilatation of the ventricles, etc., will be revealed. The weight of the brain, according to Bischoff, is 380 grams.

It is normally much softer and pinker than in the adult, the pia more delicate; both may be much congested or anemic without known cause. The ventricles contain very little serum. Malformations, apoplexies, hydrocephalus, simple and tuberculous inflammatory lesions, are to be looked for.

The Spinal Cord.—Extravasations of blood between the membranes of the cord may occur from the same causes as those in the brain. Spina bifida is the most frequent malformation.

The Thorax and Abdomen.—These are opened as in the adult. The *peritoneal cavity* contains a very little clear serum A red fluid may be produced by decomposition. The peritoneum is often the seat of intra-uterine inflammation.

The Diaphragm.—In still-born infants its convexity reaches to the fourth or fifth rib. After respiration it reaches a point between the fourth and seventh ribs. Its position is, however, so variable that it is of little diagnostic importance.

The Thorax.—The *thymus gland,* at this period very large, occupies the upper portion of the anterior mediastinum, covering the trachea and large vessels. Its average weight is about 13 grams. It is usually about 5 cm. long, 3.8 cm. wide at its lower part, and about 0.63 to 0.85 cm. in thickness. It may be hypertrophied and compress the large vessels, or be inflamed and suppurating.

The *heart* lies more nearly in the median line than in the adult. It weighs from 20 to 24 grams. The ventricular walls are of nearly equal thickness. The pericardium contains very little serum. A considerable quantity of red fluid may accumulate here as a result of decomposition. There may be small extravasations of blood beneath the pericardium in still-born children and in those born alive. Pericarditis with effusion of serum and fibrin, and endocarditis with consequent changes in the valves, may exist before birth. Malformations and malpositions of the heart and large vessels are not infrequent. Small soft reddish nodules may be present on the edges of the valves, which are remnants of the fetal mucous tissue but may be mistaken for the marks of endocarditis. The time of closure of the foramen ovale and the ductus arteriosus varies very widely in different cases.

The *pleural cavities* contain very little serum, but decomposition may lead to the accumulation of a considerable quantity of red fluid. Small extravasations of blood in the subpleural tissue may be found in children who have died before birth and after protracted labors. Inflammation, with exudation of serum, fibrin, and pus, may exist before birth.

The *lungs* in a still-born child are small, do not cover the heart, are situated in the upper and posterior portions of the thorax, are of a dark red color and of firm, liver-like consistence, and do not crepitate. In a child born alive, which has respired freely, the lungs fill the thoracic cavity, but do not cover the heart as much as in the adult; they are of a light red or pink color, and crepitate on pressure. If respiration has been incompletely performed, we find various intermediate conditions between the fetal and inflated states.

If any doubt exists as to respiration having taken place, it is customary to employ the *hydrostatic test.* This is done by placing the lungs, first together, then separately, and afterward cut into small pieces, in water. It is commonly said that if they sink the child has not breathed; if they float it has. This test is not, however, a certain one.[1]

The lesions of inflammation, and vesicular and subpleural emphysema, may be found in the lungs of new-born children.

The *pharynx* should be opened and examined for foreign bodies.

The *larynx* and *trachea* should be examined for the lesions of inflammation and for injuries to the cartilages.

The *thyroid gland* weighs about 12 grams. It may be so enlarged as to interfere with respiration.

[1] See works on medical jurisprudence.

The Abdomen.—The *kidneys* are lobulated and proportionately larger than in the adult. Thoma estimates the average weight of both organs together as 23.6 grams. There may be ecchymoses on their surface; inflammation; deposits of uric acid and urates in the tubules of the pyramids; cystic dilatation of the tubules, sometimes reaching an enormous size. There may be absence or retarded development of one kidney. Malformations and malpositions of the kidneys are of frequent occurrence.

The *adrenals* are large. They may be dilated into large cysts filled with blood.

The *spleen* is large and firm. Its average weight is about 11 grams. It may be abnormally enlarged, and its surface is sometimes covered with fresh inflammatory exudations.

The Intestines.—In the small intestines, inflammation and swelling and pigmentation of the solitary and agminated follicles (lymph-nodules) are sometimes found. The large intestine usually contains meconium, but this may be evacuated before or during birth. The sigmoid flexure is not so marked as in the adult.

The formation of gas in the stomach and intestines does not usually take place until respiration is established. If decomposition has commenced, however, gas may be formed as a part of the process.

The *liver* is of a dark red color, is large, and contains much blood. Its size diminishes after respiration is established. Its average weight is 118 grams. The size is so variable, before and after respiration, that it gives little information as to the age of the child. Large extravasations of blood are sometimes found beneath the capsule of the liver without known cause. A variety of pathological conditions, fatty and waxy degeneration, gummy tumors, etc., may be found.

The *bladder* may be full or empty, both in still-born children and in those which have breathed. Dilatation and hypertrophy may exist during intrauterine life.

Generative Organs.—The external generative organs in both males and females are more prominent than in adults. The ovaries are high up in the pelvis and large; the cervix uteri is long; the body small and lax, resting forward against the bladder. Phimosis in the males is the normal condition. Malpositions and retarded development of the testicles should be noticed. It should be observed whether the anus is perforate.

The bones, in suspected cases, should be examined for the lesions of inflammation, rickets, and syphilis.

Preservation.—The various fetal tissues may be preserved by the same methods as are employed for those of the adult; but as they are very delicate they should be handled with great care and the preservative fluids changed with sufficient frequency.

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